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Patent and Trademark Office

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Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).

Please search for a method of treating a
 proliferation disorder comprising transplanting a cell
 matrix structure comprising a gene encoding
 an anti-angiogenic molecule.

see claims 1-7

Point of Contact:
 Beverly Shears
 Technical Info. Specialist
 OWI Tel: 308-4334
 EES

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Date completed: 11-19-01
 Searcher: Beverly 4994
 Terminal time: 301
 Elapsed time: _____
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 Total time: 45
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 _____ Dialog
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 _____ Geninfo
 _____ SDC
 _____ DARC/Questel
 _____ Other

Davis, N.
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(FILE - 'REGISTRY' ENTERED AT 14:21:36 ON 19 NOV 2001)

E THROMBOMODULIN/CN 5

L2 59 S THROMBOMODULIN ?/CN

- key terms

(FILE - 'CAPLUS' ENTERED AT 14:21:54 ON 19 NOV 2001)

L2 59 SEA FILE=REGISTRY ABB=ON PLU=ON THROMBOMODULIN ?/CN
L7 373122 SEA FILE=CAPLUS ABB=ON PLU=ON NEOPLASI# OR PROLIFERAT?(
3A) (CELL OR FIBROBLAST OR SKIN OR DERMAL? OR DERMAT? OR
DISORDER OR DISEAS?) OR KELOID? OR ADHESION OR ENDOMETRIO
S? OR (CONGENITAL OR ENDOCRIN?) (3A) ABNORMAL? OR PSORIAS?
OR ARTHRITIS OR RA OR MULTIPLE SCLEROSIS OR MS(S) SCLEROSI
S OR ANGIOGENES? OR RESTENOSIS
L8 4407 SEA FILE=CAPLUS ABB=ON PLU=ON L7 AND (L2 OR THROMBOMODU
LIN OR THROMBO MODULIN OR ?ANGIOGENIC?)
L9 549 SEA FILE=CAPLUS ABB=ON PLU=ON L8 AND (MATRIX OR
MATRIC?)
L10 44 SEA FILE=CAPLUS ABB=ON PLU=ON L9 AND IMPLANT?
L11 19 SEA FILE=CAPLUS ABB=ON PLU=ON L10 AND (TREAT? OR
THERAP?)

L2 59 SEA FILE=REGISTRY ABB=ON PLU=ON THROMBOMODULIN ?/CN
L7 373122 SEA FILE=CAPLUS ABB=ON PLU=ON NEOPLASI# OR PROLIFERAT?(
3A) (CELL OR FIBROBLAST OR SKIN OR DERMAL? OR DERMAT? OR
DISORDER OR DISEAS?) OR KELOID? OR ADHESION OR ENDOMETRIO
S? OR (CONGENITAL OR ENDOCRIN?) (3A) ABNORMAL? OR PSORIAS?
OR ARTHRITIS OR RA OR MULTIPLE SCLEROSIS OR MS(S) SCLEROSI
S OR ANGIOGENES? OR RESTENOSIS
L12 44583 SEA FILE=CAPLUS ABB=ON PLU=ON L7(S) (TREAT? OR THERAP?)
L13 1089 SEA FILE=CAPLUS ABB=ON PLU=ON L12 AND (L2 OR THROMBOMOD
ULIN OR THROMBO MODULIN OR ?ANGIOGENIC?)
L14 104 SEA FILE=CAPLUS ABB=ON PLU=ON L13 AND (MATRIX OR
MATRIC##)
L15 9 SEA FILE=CAPLUS ABB=ON PLU=ON L14 AND IMPLANT?

L16- 19 L11-OR L15

L16 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:750168 CAPLUS

TITLE: Treatment with low-dose
interferon-.alpha. restores the balance between
matrix metalloproteinase-9 and
E-cadherin expression in human transitional cell
carcinoma of the bladder

AUTHOR(S): Slaton, Joel W.; Karashima, Takashi; Perrotte,
Paul; Inoue, Keiji; Kim, Sun J.; Izawa,
Jonathan; Kedar, Daniel; McConkey, David J.;
Millikan, Randall; Sweeney, Paul; Yoshikawa,
Chiaki; Shuin, Taro; Dinney, Colin P. N.

CORPORATE SOURCE: Departments of Cancer Biology, The University of
Texas M. D., Houston, TX, 77030, USA

SOURCE: Clin. Cancer Res. (2001), 7(9), 2840-2853
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Tumor invasion and metastasis are regulated by the expression of genes such as E-cadherin, which regulates cell **adhesion**, and **matrix** metalloproteinase-9 (MMP-9), which alters the integrity of the extracellular **matrix**. Both up-regulation of MMP-9 and down-regulation of E-cadherin correlate with bladder cancer metastasis. The purpose of this study was first to det. whether an imbalance between MMP-9 and E-cadherin expression correlates with metastasis from human transitional cell carcinoma (TCC) of the bladder after **therapy** with neoadjuvant chemotherapy and radical cystectomy and then to det. whether **treatment** of human TCC xenografts growing in nude mice with interferon (IFN)-.alpha. would restore this balance, thereby limiting tumor invasion and metastasis. We used in situ hybridization to evaluate the expression of several metastasis-related genes, including MMP-9 and E-cadherin, in paraffin-embedded biopsy specimens from 55 patients with muscle-invasive TCC **treated** with neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin chemotherapy and radical cystectomy. By multivariate anal., an MMP-9:E-cadherin ratio of > 1.8 was an independent prognostic factor for disease progression. In vitro incubation of an IFN-resistant, highly metastatic human TCC cell line, 253J B-VR with noncytostatic concns. of IFN-.alpha. down-regulated the activity of MMP-9, up-regulated E-cadherin, and inhibited in vitro invasion. 253J B-VR cells were **implanted** into the bladders of athymic nude mice. Systemic **therapy** with IFN-.alpha. (10,000 units s.c. daily) decreased the expression of MMP-9, increased expression of E-cadherin, reduced tumor vol., and inhibited metastasis. The MMP-9:E-cadherin ratio was 4.5 in untreated controls and 1.1 after IFN-.alpha. **treatment**. Moreover, systemic low-dose daily IFN-.alpha. potentiated the efficacy of paclitaxel. These studies indicate that in addn. to its antiproliferative and **antiangiogenic** effects, IFN-.alpha. limits tumor invasion by restoring the normal balance between MMP-9 and E-cadherin and enhances the activity of systemic chemotherapy.

L16 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:565104 CAPLUS

DOCUMENT NUMBER: 135:127275

TITLE: Delivery of **therapeutic** biological
from **implantable** tissue
matrices

INVENTOR(S): Vacanti, Joseph P.; Donahoe, Patricia K.;
MacLaughlin, David T.; Masiakos, Peter T.

PATENT ASSIGNEE(S): General Hospital Corporation, USA

SOURCE: PCT Int. Appl., 46 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001055212	A2	20010802	WO 2001-US2694	20010126
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ,			

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PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ,
UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,
TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD,
TG

PRIORITY APPLN. INFO.:

US 2000-178842 P 20000127

AB Normal cells, such as fibroblasts or other tissue or organ cell types, are genetically engineered to express biol. active, **therapeutic** agents, such as proteins that are normally produced in small amts., for example, MIS (mullerian inhibiting substance), or other members of the TGF-beta family HerceptinTM, interferons, and anti-**angiogenic** factors. These cells are seeded into a **matrix** for **implantation** into the patient to be **treated**. Cells may also be engineered to include a lethal gene, so that **implanted** cells can be destroyed once **treatment** is completed. Cells can be **implanted** in a variety of different **matrixes**. In a preferred embodiment, these **matrixes** are **implantable** and biodegradable over a period of time equal to or less than the expected period of **treatment**, when cells engraft to form a functional tissue producing the desired biol. active agent. Ovarian cancer cell lines that were responsive to MIS in vitro were place beneath th renal capsules of mice. CHO B9 cells seeded onto a polyglycolic acid **matrix** and were **implanted** in the mice. MIS produced by th B9 cells significantly inhibited the growth of the human ovarian cancer cell line in vivo.

L16 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:561826 CAPLUS

DOCUMENT NUMBER: 135:287274

TITLE: Evidence of IL-18 as a novel **angiogenic** mediator

AUTHOR(S): Park, Christy C.; Morel, Jacques C. M.; Amin, M. Asif; Connors, Matthew A.; Harlow, Lisa A.; Koch, Alisa E.

CORPORATE SOURCE: Department of Medicine, Northwestern University Medical School, Chicago, IL, 60611, USA

SOURCE: J. Immunol. (2001), 167(3), 1644-1653
CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Angiogenesis**, or new blood vessel growth, is a key process in the development of synovial inflammation in rheumatoid **arthritis** (RA). Integral to this pathol. proliferation are proinflammatory cytokines. The authors hypothesized a role for IL-18 as an **angiogenic** mediator in RA. The authors examd. the effect of human IL-18 on human microvascular endothelial cell (HMVEC) migration. IL-18 induced HMVEC migration at 1 nM. RA synovial fluids potentially induced endothelial cell migration, but IL-18 immunodepletion resulted in a 68% decrease in HMVEC migration. IL-18 appears to act on HMVECs via .alpha.v.beta.3 integrin. To test whether IL-18 induced endothelial cell tube formation in vitro, the authors quantitated the degree of tube formation on Matrigel **matrix**

IL-18, 1 or 10 nM, resulted in a 77% or 87% increase in tube formation compared with control. To det. whether IL-18 may be **angiogenic** in vivo, the authors **implanted** IL-18 in Matrigel plugs in mice, and IL-18 at 1 and 10 nM induced **angiogenesis**. The **angiogenesis** obsd. appears to be independent of the contribution of local TNF-.alpha., as evidenced by adding neutralizing anti-TNF-.alpha. Ab to the Matrigel plugs. In an alternative in vivo model, sponges embedded with IL-18 or control were **implanted** into mice. IL-18 (10 nM) induced a 4-fold increase in **angiogenesis** vs the control. These findings support a novel function for IL-18 as an **angiogenic** factor in RA and may elucidate a potential **therapeutic** target for **angiogenesis** -directed diseases.

REFERENCE COUNT:

52

REFERENCE(S):

- (1) Brooks, P; Science 1994, V264, P569 CAPLUS
- (2) Cao, R; FASEB J 1999, V13, P2195 CAPLUS
- (4) Dinarello, C; J Allergy Clin Immunol 1999, V103, P11 CAPLUS
- (5) Dinarello, C; J Leukocyte Biol 1998, V63, P658 CAPLUS
- (10) Friedlander, M; Science 1995, V270, P1500 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:452816 CAPLUS

DOCUMENT NUMBER: 135:51137

TITLE: Polymeric membrane devices for **implantation** of cell culture

INVENTOR(S): Harpstead, Stanley D.

PATENT ASSIGNEE(S): Rst Implanted Cell Technology, Llc, USA

SOURCE: PCT Int. Appl., 19 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001043696	A2	20010621	WO 2000-US42628	20001206
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 1999-464560 A 19991216

AB The invention provides a device and method for **implanting** a cell culture in a host. The device includes a biocompatible deformable body, a biocompatible microporous membrane and sealable port. In one embodiment, the device includes an attachment coating

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covering a surface microporous membrane that facilitates attachment of cells to the microporous membrane. In another embodiment, the device includes an **angiogenic** coating. The invention also provides a method for **implanting** a cell culture in a host, administering a **therapeutic** substance to a host and a method of **treating** a disease using the device.

L16 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:416980 CAPLUS

DOCUMENT NUMBER: 135:15095

TITLE: In situ bioreactors expressing systematically available bioactive agents and methods of use thereof in **therapy**

INVENTOR(S): Pierce, Glenn; Chandler, Lois Ann

PATENT ASSIGNEE(S): Selective Genetics, Inc., USA

SOURCE: PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001040272	A2	20010607	WO 2000-US32754	20001130
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 1999-168470 P 19991201

AB The present invention relates to a method of in vivo, sustained gene **therapy** wherein one or more in situ bioreactors (or neo-organoids) express systematically available bioactive agents. One method involves **implanting** or placing into a tissue site a biocompatible substance capable of cellular ingrowth (e.g., device, **matrix**, semi-permeable membrane with a **matrix** or liq. interior, etc.). and systemic delivery of a bioactive factor. Also provided are compns., devices, and kits comprising the same. In various embodiments the biocompatible substance comprises a **matrix** and at least one nucleic acid mol. encoding a bioactive agent. In other embodiments bioreactors are provided wherein a first gene that encodes a growth factor is present and a second gene encoding a bioactive agent is present during manuf. or provided to the bioreactor following manuf. or **implantation**.

L16 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:227334 CAPLUS

DOCUMENT NUMBER: 135:3796

TITLE: Angiopoietin-2 is related to tumor **angiogenesis** in gastric carcinoma:

possible in vivo regulation via induction of proteases

AUTHOR(S): Etoh, Tsuyoshi; Inoue, Hiroshi; Tanaka, Shinji; Barnard, Graham F.; Kitano, Seigo; Mori, Masaki

CORPORATE SOURCE: Department of Surgery, Medical Institute of Bioregulation, Kyushu University, Beppu, 874-0838, Japan

SOURCE: Cancer Res. (2001), 61(5), 2145-2153
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Tumor **angiogenesis** progresses by a dynamic balance between tumor vascular regression and growth. Angiopoietin (Ang)-2 (the natural antagonist for the **angiogenic** Tie-2 receptor) and vascular endothelial growth factor (VEGF) are thought to be crit. regulators in this process; therefore, these may play a crit. role in cancer aggressiveness. The aim of this study was to clarify the clin. and biol. significance of the expression of Ang-2 in human gastric cancers and to investigate the relationship between Ang-2 together with VEGF and the induction of proteases such as **matrix** metalloproteinases (MMPs) in the process of tumor development. Eighty-five individuals with gastric cancer, who had undergone surgery without preoperative **treatment**, were studied. A stable transfectant of the human MKN-7 gastric cancer cell lines with an Ang-2 expression vector was used for the exptl. study. First, we examd. the relationship between the mRNA expression of Angs by Northern blot anal. and clinicopathol. features. High Ang-2-expression cases showed more frequent vascular involvement and more advanced stages of disease compared with low Ang-2-expression cases ($P < 0.05$). With regard to prognosis, the survival time for patients in the high-Ang-2 mRNA group was significantly shorter ($P < 0.05$). When we examd. the localization of Ang-2 in human gastric cancers, immunohistochem. anal. revealed that this protein was expressed predominantly in cancer tissues when compared with normal tissues. Interestingly it was expressed not only in endothelia cells (ECs) but also in cancer cells. Second, Ang-2-transfected cells were **implanted** in vivo into the gastric walls of nude mice. Ang-2-transfectant mice developed highly metastatic tumors with hypervascularity as compared with MKN-7 or control vector-transfectant tumors. There was a significant correlation between Ang-2 mRNA expression and lower grade of vessel maturation. Third, on the basis of the in vivo data, we focused on prodn. of proteases such as MMPs to investigate possible mechanisms in these processes. MMP-1, MMP-9, and urokinase-type plasminogen activator in ECs were strongly up-regulated by Ang-2 in the presence of VEGF in vitro. These data suggest that prodn. of Ang-2 is implicated in tumor development in human gastric cancers. Its prodn. may contribute to tumor **angiogenesis** by induction of proteases in ECs, which may be enhanced in the presence of VEGF.

REFERENCE COUNT: 42

REFERENCE(S): (2) Bacharach, E; Proc Natl Acad Sci USA 1992, V89, P10686 CAPLUS
(4) Davis, S; Cell 1996, V87, P1161 CAPLUS
(5) Davis, S; Curr Top Microbiol Immunol 1999, V237, P173 CAPLUS
(6) Dumont, D; Oncogene 1992, V7, P1471 CAPLUS

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(8) Folkman, J; Nat Med 1995, V1, P27 CAPLUS
ALL CITATIONS AVAILABLE IN THE -RE FORMAT

L16 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:120250 CAPLUS

DOCUMENT NUMBER: 134:232031

TITLE: Fibroblast growth factor 2 activation of stromal
cell vascular endothelial growth factor
expression and **angiogenesis**

AUTHOR(S): Claffey, Kevin P.; Abrams, Kristin; Shih,
Shu-Ching; Brown, Lawrence F.; Mullen, Andrew;
Keough, Martin

CORPORATE SOURCE: Center for Vascular Biology, University of
Connecticut Health Center, Farmington, CT,
06030, USA

SOURCE: Lab. Invest. (2001), 81(1), 61-75

CODEN: LAINAW; ISSN: 0023-6837

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Angiogenesis** is a key component of human cancer progression and metastasis. In an effort to recapitulate early events in tumor-induced **angiogenesis**, the authors have employed a s.c. Matrigel **implant** model using immunodeficient mice as hosts. Matrigel-contg. fibroblast growth factor 2 (FGF-2; 1.2 .mu.g/mL) induced stromal cell infiltration into the Matrigel/skin interface within 4 days and maximal neovascularization at 7 days. Cells staining pos. for the endothelial cell marker, platelet-endothelial cell **adhesion** mol. 1 (PECAM-1), were present in neovessels and in isolated cells within the Matrigel **matrix**. Immunohistochem. anal. revealed high levels of vascular endothelial growth factor (VEGF) deposited in the stromal interface present only in the FGF-2-contg. but not in control Matrigel **implants**. VEGF expression was confirmed with in situ hybridization. High VEGF mRNA levels were obsd. in the infiltrating stromal cells but not in endothelial or endothelial precursors as defined by PECAM-1 staining. In vitro anal. of FGF-2-**treated** embryonic fibroblasts, Balb/c 3T3 cells, showed an induction of VEGF transcription, mRNA synthesis, and protein secretion as defined by transcriptional reporter, Northern blot, and ELISA assays. The FGF-2-induced VEGF expression was not dependent on select **matrix** adherence or signaling components because VEGF mRNA expression induced by FGF-2 was equally activated on serum, basement membrane, and fibronectin **matrix** substrates. Systemic application of anti-VEGF antibodies significantly repressed FGF-2-induced **angiogenesis** over control antibody by 88%. These data support an FGF-2 **angiogenic** model that is dependent on endothelial cell activation, stromal cell infiltration, and VEGF expression by the infiltrating stromal cell population.

REFERENCE COUNT: 92

REFERENCE(S): (1) Abdulrauf, S; J Neurosurg 1998, V88, P513
CAPLUS

(3) Andrade, S; Microvasc Res 1997, V54, P253
CAPLUS

(5) Asano, M; Cancer Res 1995, V55, P5296 CAPLUS

(7) Banai, S; Cardiovasc Res 1994, V28, P1176
CAPLUS

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(10) Berger, W; Int J Cancer 1999, V83, P415
CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:12589 CAPLUS

DOCUMENT NUMBER: 134:76442

TITLE: Compositions containing growth factors and
methods for forming and strengthening bone

INVENTOR(S): Marchosky, J. Alexander

PATENT ASSIGNEE(S): USA

SOURCE: PCT Int. Appl., 41 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000792	A1	20010104	WO 2000-US17955	20000629
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 1999-141386 P 19990629

AB Comps. for stimulating bone growth comprise (a) growth factors, (b) demineralized, non-decalcified bone **matrix**, (c) a scaffolding material selected from cancelous bone, chitosan, chitosan-protein, and chitosan-protein fibers, and (d) a gel material selected from chitosan and its derivs., alginate, or hyaluronic acid. Addnl., comps. may contain **angiogenesis** -stimulating materials and osteoinductive materials. Methods for utilizing the comps. for filling in bone defects, promoting rapid fusion of bone fractures, grafts, and bone-prostheses, and promoting strengthening of osteoporotic bones are also provided. For example, bone formation at the site of bone defect was obsd. 12 wk after the application of the compn. contg. demineralized bone **matrix**, hyaluronic acid, and vascular endothelial growth factor.

REFERENCE COUNT: 2

REFERENCE(S): (1) Glowacki; US 4440750 A 1984 CAPLUS
(2) Weinberg; US 4837379 A 1989 CAPLUS

L16 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:772684 CAPLUS

DOCUMENT NUMBER: 133:340251

TITLE: Polymeric encapsulation system promoting
angiogenesis

INVENTOR(S): Prokop, Ales; Davidson, Jeffrey M.; Dikov, Mikhail M.; Williams, Phillip

PATENT ASSIGNEE(S): Vanderbilt University, USA

SOURCE: PCT Int. Appl., 43 pp.

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CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000064954	A1	20001102	WO 2000-US10698	20000419
W: AU, CA, CN, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

PRIORITY APPLN. INFO.: US 1999-130615 P 19990422

AB The present invention provides a convenient polymeric film or microparticulate vehicle to deliver protein factors into appropriate body sites to induce appropriate **therapeutic** effects. It also improves the existing methodologies for immunoisolation of non-human pancreatic islets (via microencapsulation) to protect them from the immunol.-different host. This invention demonstrates how vascularization and **angiogenesis** can be induced by means of addn. of proper **angiogenic** factors. The **angiogenesis** is sustained over a long period of time, depending on the release characteristics of the polymeric **matrix**. Three-dimensional polymeric structures (mesh or perforated tubing and film) are used as resident materials for microcapsules bearing islets. Blood capillaries are generated outside the capsules and penetrate through the **implant** openings to in-grow into the vicinity of capsules/islets. Thus, Polymer films were prepd. from cellulose sulfate and sodium alginate, CaCl₂ and poly(methylene-co-guanidine) hydrochloride and coated with CM-cellulose and alginate. The core soln. contained an addnl. ingredient: 0.1-15 .mu.g/mL bFGF. The gelled film contained almost all quantity of the factor supplied. The leakage of this factor to the external cationic bath was essentially zero due to the fact that this **angiogenesis** stimulating factor is about 15,000 daltons in size, larger than the mol. cut-off of the dialysis membrane. This was confirmed in another expt. by using 125I-labeled factor. This film product presents a distinct advantage compared to the small encapsulation efficiency obsd. with std. microencapsulation technol.

REFERENCE COUNT: 3
REFERENCE(S): (1) Desai; US 5334640 A 1994 CAPLUS
(2) Hubbell; US 5567440 A 1996 CAPLUS
(3) Hubbell; US 5858746 A 1999 CAPLUS

L16 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:700322 CAPLUS

DOCUMENT NUMBER: 133:359006

TITLE: An experimental study in the chick embryo chorioallantoic membrane of the anti-**angiogenic** activity of cyclosporine in rheumatoid **arthritis** versus osteoarthritis

AUTHOR(S): Ribatti, D.; Vacca, A.; Cantatore, F. P.; Ria, R.; Benagiano, V.; Roncali, L.; Dammacco, F.

CORPORATE SOURCE: Department of Human Anatomy and Histology, Medical School, University of Bari, Bari, 70124, Italy

Searcher : Shears 308-4994

09/822161

SOURCE: Inflammation Res. (2000), 49(8), 418-423
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Angiogenesis** plays an important role in the pathogenesis of rheumatoid arthritis (RA) and correlates with clin. score, synovial hyperplasia and infiltration of inflammatory cells. Many of the available **treatments** for RA have been shown to possess some degree of anti-**angiogenic** activity. The authors studied the effect of cyclosporine, which exerts anti-**angiogenic** activity in vitro and in vivo [1] on **angiogenesis** induced in vivo in the chick embryo chorioallantoic membrane (CAM) by synovial RA and osteoarthritis (OA) tissues. Wet synovial biopsies from 10 RA and 6 OA patients were **treated** with vehicle alone or with cyclosporine and **implanted** on the CAM at day 8 of incubation. On day 12, CAM tissues were assessed for the extent of **angiogenesis** and mononuclear cell infiltration. Cyclosporine inhibited **angiogenesis** and reduced the no. of mononuclear cells in the CAM extracellular **matrix** only in RA implants. These data provide further evidence for a central role of new-formed blood vessels in RA. Moreover, cyclosporine on account of both its immunosuppressive and its anti-**angiogenic** activity can be proposed for the **treatment** of RA.

REFERENCE COUNT: 42
REFERENCE(S): (3) Blotnick, S; Proc Natl Acad Sci 1994, V91, P2890 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:136298 CAPLUS
DOCUMENT NUMBER: 133:38169
TITLE: Inhibition of corneal neovascularization by .alpha.v-integrin antagonists in the rat
AUTHOR(S): Klotz, Oliver; Park, Joon-Keun; Pleyer, Uwe; Hartmann, Christian; Baatz, Holger
CORPORATE SOURCE: Department of Ophthalmology, University Hospital Charite, Berlin, D-13353, Germany
SOURCE: Graefe's Arch. Clin. Exp. Ophthalmol. (2000), 238(1), 88-93
CODEN: GACODL; ISSN: 0721-832X
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: The **proliferation** of vascular endothelial cells and ultimately **angiogenesis** is inhibited by blocking integrin-mediated cell-**matrix** interaction. To asses the **therapeutic** potential of .alpha.v-integrin antagonists LM609 and cRGDFv in neovascularization of the anterior

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segment, their inhibitory effect on **angiogenesis** was studied in two rat models for corneal neovascularization. Methods: Corneal neovascularization was induced in Wistar rats (n=51) either by silver nitrate burns or intrastromal **implantation** of polymer pellets contg. 400 ng of fibroblast growth factor (bFGF). Animals were **treated** with s.c. injections of a cyclic .alpha.v-integrin antagonist (cRGDFV, 15 mg/kg body wt.) or saline twice daily. Addnl. animals received intrastromal **implants** contg. 400 ng bFGF together with either LM609 (mAb, anti-.alpha.v.beta.3) or control antibody. Four days later, the animals were killed and the percentage of the surface area covered with vessels detd. using digital image anal. Results: Systemic **treatment** with cRGDFV resulted in a significant redn. of corneal vessel growth in animals with bFGF-induced corneal vascularization. In corneas with silver nitrate burns, systemic cRGDFV **treatment** showed no significant redn. of vascularization compared with controls. Pellets contg. bFGF and LM609 mAb induced significantly less neovascularization than pellets contg. bFGF and control mAb. Conclusion: Our results suggest that in the rat cornea, .alpha.v.beta.3 ligation does inhibit bFGF-induced neovascularization. A chem. burn of the cornea induces **angiogenesis** which is not inhibited by blocking .alpha.v-integrins. This suggests an **angiogenic** pathway independent of .alpha.v-integrins.

REFERENCE COUNT:

21

REFERENCE(S):

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- (2) Brooks, P; Science 1994, V264, P569 CAPLUS
- (4) Enenstein, J; J Invest Dermatol 1994, V103, P381 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:736893 CAPLUS

DOCUMENT NUMBER: 131:332976

TITLE: Sustained dna delivery from structural porous **matrices** for gene **therapy** applications with special emphasis is on bone formation and regeneration

INVENTOR(S): Shea, Lonnie D.; Bonadido, Jeffrey; Mooney, David J.

See priority info.

PATENT ASSIGNEE(S): The Regents of the University of Michigan, USA

SOURCE: PCT Int. Appl., 144 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958656	A2	19991118	WO 1999-US10330	19990512
WO 9958656	A3	20000106		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN,

	IS,	JP,	KE,	KG,	KP,	KR,	KZ,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	MD,
	MG,	MK,	MN,	MW,	MX,	NO,	NZ,	PL,	PT,	RO,	RU,	SD,	SE,	SG,	SI,
	SK,	SL,	TJ,	TM,	TR,	TT,	UA,	UG,	UZ,	VN,	YU,	ZW,	AM,	AZ,	BY,
	KG,	KZ,	MD,	RU,	TJ,	TM									
RW:	GH,	GM,	KE,	LS,	MW,	SD,	SL,	SZ,	UG,	ZW,	AT,	BE,	CH,	CY,	DE,
	DK,	ES,	FI,	FR,	GB,	GR,	IE,	IT,	LU,	MC,	NL,	PT,	SE,	BJ,	BJ,
	CF,	CG,	CI,	CM,	GA,	GN,	GW,	ML,	MR,	NE,	SN,	TD,	TG		

AU 9938986	A1	19991129	AU 1999-38986		19990512
PRIORITY APPLN. INFO.:			US 1998-85305	P	19980513
			US 1998-109054	P	19981119
			WO 1999-US10330	W	19990512

AB Disclosed are particular 3-dimensional structural **matrixes** contg. DNA and their use in the prolonged release of DNA in various biol. environments. The structural **matrix** is a porous polymer [PLGA]-based contg. pores formed by gas foaming involving inert gases (CO₂) and leaching out of a water-sol. particulate (salt, NaCl, sugar, glucose, sucrose, mannitol) when exposed to body fluids. The admixt. is compression molded into a selected size and shape prior to executing the gas foaming process. The structural **matrix** may also be an alginate or modified alginate **matrix**. This structural **matrix** is a biocompatible or biodegradable **matrix**. It may also be a lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid copolymer **matrix**. At least part of this **matrix** may be comprised of lactic acid/glycolic acid (PLGA) copolymer **matrix**. The structural **matrix** may be modified where one side section is bonded to one cell interaction mol. such as cell **adhesion** mols., cell attachment peptides, proteoglycan attachment peptide sequences, proteoglycans, cell **adhesion** polysaccharides, growth factors, cell **adhesion** enzymes, RGD peptide, fibronectin, vitronectin, Laminin A, Laminin B1, Laminin B2, collagen 1 and thrombospondin. The DNA-**matrix** materials are created such that they maintain a defined space, allowing cellular migration, transfection and proliferation to occur in a controlled manner. Such DNA-contg. structural **matrixes** are thus particularly useful in in vivo cell transfection and gene expression in the context of gene **therapy**. This may encode a protein for stimulating bone progenitors or wound healing in fibroblast or in tissue or organ regeneration or transplantation or an antigen for immunity or cytotoxic or apoptosis-inducing protein or a transcription factor or elongation factor or cell cycle control protein or kinase or phosphatase or DNA repair protein or oncogene or tumor suppressor or **angiogenic** protein or anti-**angiogenic** protein or immune response stimulating protein or cell surface receptor or accessory signaling mol. or transport protein or anti-bacterial or anti-viral protein or hormone or neurotransmitter or growth factor or growth factor receptor or interferon or interleukin or chemokine or cytokine or colony stimulating factor or chemotactic factor protein of growth hormone or parathyroid hormone or PTH1-34 polypeptide or bone morphogenic protein or BMP-2A or BMP-2B or BMP-3 or BMP-4 or BMP-5 or BMP-6 or BMP-7 or BMP-8 or TGF-.alpha. or TGF-.beta.1 or TGF-.beta.2 or latent TGF.beta. binding protein or activin/inhibin protein or FGF or GMCSF or EGF or PDGF or insulin-like growth factor or leukemia inhibitory factor. This method allows for the use in gene transfer to cells within a tissue site and in manuf. of a medicament for gene **therapy**. **Implantable** medical devices comprising this gene-

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matrix are described. The release of nucleic acids from the **matrix** is controlled by diffusion. This method also applies to cancer **therapy** or **treating** viral infection.

L16 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:735669 CAPLUS

DOCUMENT NUMBER: 132:202726

TITLE: Interferon-.alpha.-mediated down-regulation of **angiogenesis**-related genes and **therapy** of bladder cancer are dependent

AUTHOR(S): on optimization of biological dose and schedule
Slaton, Joel W.; Perrotte, Paul; Inoue, Keiji;
Dinney, Colin P. N.; Fidler, Isaiah J.

CORPORATE SOURCE: Department of Cancer Biology, Anderson Cancer
Center, The University of Texas M. D., Houston,
TX, 77030, USA

SOURCE: Clin. Cancer Res. (1999), 5(10), 2726-2734

CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The purpose of this study was to identify and optimize the **antiangiogenic** activity of IFN-.alpha. against human bladder cancer cells growing in the bladder of nude mice. 253J B-V IFNR cells (resistant to antiproliferative effects of IFN-.alpha. or IFN-.beta.) were **implanted** into the bladder wall of nude mice. Three days later, the mice were **treated** with s.c. injections of IFN-.alpha. (70,000 units/wk) at different dosing schedules (1, 2, 3, or 7 times/wk). Daily **therapy** with IFN-.alpha. produced the most significant inhibition of tumor growth, tumor vascularization, and down-regulation of basic fibroblast growth factor and **matrix** metalloprotease-9 mRNA and protein expression. Changing dose and schedule of IFN-.alpha. administration had minimal effects on the expression of vascular endothelial growth factor or interleukin 8. The daily s.c. administrations of 5,000 or 10,000 units IFN-.alpha.-2a produced maximal inhibition of bFGF and MMP-9 expression (mRNA and protein), maximal redn. in tumor vessel d., and maximal redn. in serum levels of bFGF. Daily administration of higher doses of IFN-.alpha. failed to produce significant **antiangiogenic** effects. These data suggest that the **antiangiogenic** activity of IFN-.alpha. is dependent on frequent administration of optimal biol. dose and not maximal tolerated dose.

REFERENCE COUNT: 77

REFERENCE(S): (1) Baron, S; Antiviral Res 1994, V24, P97
CAPLUS
(2) Baron, S; J Am Med Assoc 1991, V266, P1375
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(8) Caruthers, M; Cold Spring Harbor Symp Quant
Biol 1982, V47, P411 CAPLUS
(10) Dinney, C; Cancer Res 1998, V58, P808
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:620008 CAPLUS

09/822161

DOCUMENT NUMBER: 132:131880
TITLE: A new synthetic **matrix**
metalloproteinase inhibitor modulates both
angiogenesis and urokinase type
plasminogen activator activity
AUTHOR(S): Shono, Tadahisa; Motoyama, Masaaki; Tatsumi,
Kunihiko; Ulbrich, Norbert; Iwamoto, Yukihide;
Kuвано, Michihiko; Ono, Mayumi
CORPORATE SOURCE: Departments of Biochemistry, Kyushu University
School of Medicine, Fukuoka, 812-8582, Japan
SOURCE: Angiogenesis (1999), Volume Date 1998-1999,
2(4), 319-329
CODEN: AGIOFT; ISSN: 0969-6970
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Proteolytic degradn. of the extracellular **matrix** is
essential to **angiogenesis**. Two families of proteases, the
serine proteases of plasminogen activator/plasmin system and the
matrix metalloproteinases (MMPs) are closely involved in
these processes. The **treatment** of mice with a diet contg.
a new synthetic MMP inhibitor, OPB-3206 (3S-[4-(N-hydroxyamino)-2R-
isobutylsuccinyl]amino-1-methoxy-3,4-dihydrocarbostyryl), abrogated
the development of new vessels in a rat corneal assay, and in a
mouse Matrigel assay. In an in vitro **angiogenesis** model,
OPB-3206 inhibited the migration and the tube formation of bovine
aortic endothelial cells at 10-100 times lower concns. than those
required to inhibit the growth of these cells. OPB-3206 as well as
other MMP inhibitory drugs, batimastat/BB-94 and marimastat/BB-2516,
also selectively inhibited tubular morphogenesis in vitro. OPB-3206
reduced the activities of interstitial collagenase and type IV
collagenase, but the concns. of 50% inhibition against these MMPs
were much higher than those of BB-94 and BB-2516. However, this new
compd. also inhibited urokinase type plasminogen activator activity
on fibrin zymogram, while BB-94 and BB-2516 did not. Furthermore,
the addn. of urokinase type plasminogen activator reduced the
inhibitory effect of the tubular morphogenesis of vascular
endothelial cells by OPB-3206. The **treatment** of mice with
a diet contg. this new compd. also reduced the growth of
implanted mammary carcinomas as well as the lung metastasis
of colon carcinoma. The anti-**angiogenic** effect of
OPB-3206 appeared to be assocd. with its inhibition of tumor growth
and metastasis.
REFERENCE COUNT: 39
REFERENCE(S): (1) Abe, T; J Clin Invest 1993, V92(1), P54
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CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT
L16 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:473511 CAPLUS
DOCUMENT NUMBER: 131:139010

Searcher : Shears 308-4994

TITLE: Broad antitumor and **antiangiogenic** activities of AG3340, a potent and selective MMP inhibitor undergoing advanced oncology clinical trials

AUTHOR(S): Shalinsky, D. R.; Brekken, J.; Zou, H.; McDermott, C. D.; Forsyth, P.; Edwards, D.; Margosiak, S.; Bender, S.; Truitt, G.; Wood, A.; Varki, N. M.; Appelt, K.

CORPORATE SOURCE: Departments of Pharmacology, Agouron Pharmaceuticals, Inc., San Diego, CA, 92121, USA

SOURCE: Ann. N. Y. Acad. Sci. (1999), 878(Inhibition of Matrix Metalloproteinases), 236-270
CODEN: ANYAA9; ISSN: 0077-8923

PUBLISHER: New York Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We studied AG3340, a potent metalloproteinase (MMP) inhibitor with pM affinities for inhibiting gelatinases (MMP-2 and -9), MT-MMP-1 (MMP-14), and collagenase-3 (MMP-13) in many tumor models. AG3340 produced dose-dependent pharmacokinetics and was well tolerated after i.p. (i.p.) and oral dosing in mice. Across human tumor models, AG3340 produced profound tumor growth delays when dosing began early or late after tumor **implantation**, although all established tumor types did not respond to AG3340. A dose-response relationship was explored in three models: COLO-320DM colon, MV522 lung, and MDA-MB-435 breast. Dose-dependent inhibitions of tumor growth (over 12.5-200 mg/kg given twice daily, b.i.d.) were obsd. in the colon and lung models; and in a third (breast), maximal inhibitions were produced by the lowest dose of AG3340 (50 mg/kg, b.i.d.) that was tested. In another model, AG3340 (100 mg/kg, once daily, i.p.) markedly inhibited U87 glioma growth and increased animal survival. AG3340 also inhibited tumor growth and increased the survival of nude mice bearing androgen-independent PC-3 prostatic tumors. In a sixth model, KKLS gastric, AG3340 did not inhibit tumor growth but potentiated the efficacy of Taxol. Importantly, AG3340 markedly decreased tumor **angiogenesis** (as assessed by CD-31 staining) and **cell proliferation** (as assessed by bromodeoxyuridine incorporation), and increased tumor necrosis and apoptosis (as assessed by hematoxylin and eosin and TUNEL staining). These effects were model dependent, but **angiogenesis** was commonly inhibited. AG3340 had a superior **therapeutic** index to the cytotoxic agents, carboplatin and Taxol, in the MV522 lung cancer model. In combination, AG3340 enhanced the efficacy of these cytotoxic agents without altering drug tolerance. Addnl., AG3340 decreased the no. of murine melanoma (B16-F10) lesions arising in the lung in an i.v. metastasis model when given in combination with carboplatin or Taxol. These studies directly support the use of AG3340 in front-line combination chemotherapy in ongoing clin. trials in patients with advanced malignancies of the lung and prostate.

REFERENCE COUNT: 72

REFERENCE(S): (1) An, Z; Clin Exp Metastasis 1997, V15, P184
CAPLUS
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CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:333884 CAPLUS

DOCUMENT NUMBER: 127:16465

TITLE: Regulation of local host-mediated antitumor mechanisms by cytokines: direct and indirect effects on leukocyte recruitment and **angiogenesis**

AUTHOR(S): Watanabe, Morihiro; McCormick, Kathryn L.; Volker, Kirk; Ortaldo, John R.; Wigginton, Jon M.; Brunda, Michael J.; Wiltrout, Robert H.; Fogler, William E.

CORPORATE SOURCE: Laboratory of Experimental Immunology, Division of Basic Sciences, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD, 21702-1201, USA

SOURCE: Am. J. Pathol. (1997), 150(5), 1869-1880

CODEN: AJPA44; ISSN: 0002-9440

PUBLISHER: American Society for Investigative Pathology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The regulation of tumor growth by cytokine-induced alterations in host effector cell recruitment and activation is intimately assocd. with leukocyte **adhesion** and **angiogenic** modulation. Here, the authors developed a novel tumor model to investigate this complex series of events in response to cytokine administration. Gelatin sponges contg. recombinant human basic fibroblast growth factor (rhFGFb) and B16F10 melanoma cells were **implanted** onto the serosal surface of the left lateral hepatic lobe in syngeneic C57BL/6 mice. The tumor model was characterized by progressive tumor growth initially localized within the sponge and the subsequent development of peritoneal carcinomatosis. Microscopic examn. of the sponge **matrix** revealed well developed tumor-assocd. vascular structures and areas of endothelial cell activation as evidenced by leukocyte margination. **Treatment** of mice 3 days after sponge **implantation** with a **therapeutic** regimen consisting of pulse recombinant human interleukin-2 (rhIL-2) combined with recombinant murine interleukin-12 (rmIL-12) resulted in a marked hepatic mononuclear infiltrate and inhibition of tumor growth. In contrast to the control group, sponges from mice **treated** with rhIL-2/rmIL-12 demonstrated an overall lack of cellularity and vascular structure. The regimen of rhIL-2 in combination with rmIL-12 was equally effective against gelatin sponge **implants** of rhFGFb/B16F10 melanoma in SCID mice **treated** with anti-asialo-GM1 in the absence of a mononuclear infiltration, suggesting that T, B, and/or NK cells were not the principal mediators of the antitumor response in this tumor model. The absence of vascularity within the sponge after **treatment** suggests that a potential mechanism of rhIL-2/rmIL-12 antitumor activity is the inhibition of neovascular growth assocd. with the establishment of tumor lesions. This potential mechanism could be dissocd. from the known activities of these 2 cytokines to induce

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the recruitment and activation of host effector cells. Moreover, this model provides a unique opportunity to study the cellular and mol. mechanism(s) underlying both tumor **angiogenesis** and leukocyte recruitment to metastatic lesions.

L16 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:189223 CAPLUS

DOCUMENT NUMBER: 126:221052

TITLE: Angiotensin-II-induced **angiogenesis** in sponge **implants** in mice

AUTHOR(S): Andrade, Silvia P.; Cardoso, Cibele C.; Machado, Rosangela D.P.; Beraldo, W.T.

CORPORATE SOURCE: Department of Physiology and Biophysics, Institute of Biological Sciences, Federal University of Minas Gerais, Belo Horizonte MG, 31270-901, Brazil

SOURCE: Int. J. Microcirc.: Clin. Exp. (1997), Volume Date 1996, 16(6), 302-307

CODEN: IMCEDT; ISSN: 0167-6865

PUBLISHER: Kluwer

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Stimulators of **angiogenesis** hold potential in promoting the development of collateral circulation in ischemic tissue and accelerating wound healing, but promote pathol. vasoformation in **angiogenesis**-dependent diseases (solid tumors, atherosclerosis). The renin-angiotensin system is implicated in both beneficial **angiogenesis** and pathol. vascular growth. We investigated the **angiogenic** activity of angiotensin II (AII) in a sponge **implant** model in mice; this peptide enhanced **angiogenesis**, as well as glycosaminoglycan (GAG, chondroitin sulfate proteoglycan) and protein synthesis in sponge **matrix** in mice in a dose-dependent fashion. Extensive **angiogenesis** was achieved with AII (1 .mu.g), which gave no significant increase in wet wt. and protein and only a small effect on GAG. In the **implants** treated with AII (2 .mu.g) no further increase in **angiogenesis** was obsd., whereas a marked effect was shown in wet wt. (326 vs. 424 mg), total protein (18 vs. 25 .mu.g/wet wt.) and GAG (98 vs. 160 ng/wet wt.). The local blood flow has been detd. by measuring the washout rate of ¹³³Xe injected into the **implants**, correlated with histol. evidence of vessel growth. This model of **angiogenesis** has allowed sequential studies of fibrovascular tissue infiltration simultaneously with histol. and biochem. parameters of **angiogenesis**.

L16 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1995:578733 CAPLUS

DOCUMENT NUMBER: 122:322585

TITLE: Local polymeric gel cellular **therapy**

INVENTOR(S): Slepian, Marvin; Massia, Stephen P.

PATENT ASSIGNEE(S): USA

SOURCE: PCT Int. Appl., 80 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

Searcher : Shears 308-4994

09/822161

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9509659	A1	19950413	WO 1994-US11304	19941006
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5575815	A	19961119	US 1993-132745	19931006
AU 9479671	A1	19950501	AU 1994-79671	19941006
AU 703003	B2	19990311		
EP 723462	A1	19960731	EP 1994-930606	19941006
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09506011	T2	19970617	JP 1994-511004	19941006
PRIORITY APPLN. INFO.:			US 1993-132745	19931006
			US 1994-238931	19940506
			US 1988-235998	19880824
			US 1990-593302	19901003
			US 1992-857700	19920325
			US 1992-987357	19921207
			US 1993-118978	19930909
			WO 1994-US11304	19941006

AB A synthetic barrier made of biocompatible polymeric materials is applied in vivo to a tissue or cellular surface such as the interior surface of a blood vessel, tissue lumen or other hollow space. The material may also be applied to tissue-contacting surfaces of **implantable** medical devices. The polymeric materials are characterized by a fluid state which allows application to, and preferably **adhesion** to, tissue lumen surfaces, which can be increased or altered to a 2nd less fluid state in situ; controlled permeability and degradability; and, in the preferred embodiments, incorporation of bioactive materials (e.g. peptides) for release in vivo, either to the tissue lumen surface or to the interior of the lumen, which alter cell-to-cell interactions. The materials may be used to prevent proliferation or migration of smooth muscle or endothelial cells and thereby prevent intimal thickening, **restenosis**, **adhesions**, etc. Tenascin is a mediator of smooth muscle cell migration through interaction with specific integrin components of the cells; the polymeric material may be used to inhibit this interaction. Thus, application of a thermoreversible, biodegradable, erodible polyether gel film to the injured intimal surface of rat aorta reduced the thrombogenicity of the intimal surface and the eventual development of neointimal hyperplasia.

L16 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1988:605125 CAPLUS

DOCUMENT NUMBER: 109:205125

TITLE: Site-directed neovessel formation in vivo

AUTHOR(S): Thompson, John A.; Anderson, Kathryn D.; DiPietro, Judith M.; Zwiebel, James A.; Zametta, Massimo; Anderson, W. French; Maciag, Thomas
CORPORATE SOURCE: Lab. Mol. Hematol., Natl. Heart, Lung Blood Inst., Bethesda, MD, 20892, USA

SOURCE: Science (Washington, D. C., 1883-) (1988), 241(4871), 1349-52

CODEN: SCIEAS; ISSN: 0036-8075

DOCUMENT TYPE: Journal

Searcher : Shears 308-4994

09/822161

LANGUAGE: English

AB To define further the **angiogenic** action of heparin-binding growth factor I (I) in vivo, the affinity of I for polypeptide components of the extracellular **matrix** was used in a manner permitting construction of site-specific neovessels in vivo. I bound to immobilized gelatin and collagen type IV. When gelatin sponges **treated** with I were **implanted** in the neck and peritoneal cavities of rats an **angiogenic** effect could be obsd. within 1 wk. Similar results were obsd. with I concns. of 1-100 ng/cm sponge. Regardless of **implantation** site, the neovascular response was composed of cells recruited from the host organs. I could also sustain growth of a rat hepatocyte cell line simultaneously **implanted** with the I-**treated** Gelfoam. I-induced site-specific neovessel formation in vivo may be useful as a host and vector for the establishment of a vascular bridge between organs and genetically manipulated cells and may be pertinent to issues of tissue graft and replacement.

(~~FILE~~ ~~UMEDLINE~~, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JTCST-EPLUS, JAPIO' ENTERED AT 14:34:06 ON 19 NOV 2001)

L17 76 S L11
L18 58 S L15
L19 76 S L17 OR L18
L20 ~~42~~ ~~DUP~~ ~~REM~~ ~~L19~~ (34 ~~DUPLICATES~~ REMOVED)

L20 ANSWER 1 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-417900 [44] WPIDS
DOC. NO. CPI: C2001-126284
TITLE: New hydrocarbon ring compounds e.g. steroids used to **treat** e.g. cancers, autoimmune disorders, inflammatory and allergic conditions, neurodegeneration or cardiovascular disorders, are steroid sulfatase inhibitors .
DERWENT CLASS: B01 C03
INVENTOR(S): HEJAZ, H; POTTER, B V L; PUROHIT, A; REED, M J
PATENT ASSIGNEE(S): (STER-N) STERIX LTD
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001044268	A1	20010621	(200144)*	EN	75
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC					
MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE					
DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG					
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ					
PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN					
YU ZA ZW					
AU 2001021906	A	20010625	(200162)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001044268	A1	WO 2000-GB4689	20001207
AU 2001021906	A	AU 2001-21906	20001207

Searcher : Shears 308-4994

FILING DETAILS:

PATENT NO	KIND	PATENT NO
-----	-----	-----
AU 2001021906 A	Based on	WO 200144268

PRIORITY APPLN. INFO: GB 2000-18040 20000721; GB 1999-29445
 19991213; GB 2000-4317 20000223

AN 2001-417900 [44] WPIDS

AB WO 200144268 A UPAB: 20010809

NOVELTY - Hydrocarbyl ring compounds (I), particularly steroid structures, active as steroid sulfatase inhibitors are new.

DETAILED DESCRIPTION - Hydrocarbyl ring compounds of formula (I), particularly steroid structures, active as steroid sulfatase inhibitors are new, (I) being capable of inhibiting steroid sulfatase (STS) activity.

X = ring of at least 4 atoms;

K' = hydrocarbyl;

Rh1, Rh2 = optional halo (with at least one of Rh1 and Rh2 being present); and

Rs = sulfamate, phosphonate, thiophosphonate, sulfonate or sulfonamide.

An INDEPENDENT CLAIM also included for a method comprising:

(a) performing a steroid sulfatase assay with one or more candidate compounds (Ia);

(b) determining whether one or more of (Ia) is/are capable of modulating or inhibiting STS activity; and

(c) selecting one or more of the candidate compounds that is/are capable of modulating or inhibiting STS activity.

ACTIVITY - Cytostatic; immunosuppressive; contraceptive; nootropic; vasotropic; neuroprotective; anticonvulsant; cerebroprotective; vulnerary; antirheumatic; antiarthritic; antidiabetic; antiinflammatory; dermatological; antithyroid; antipsoriatic; antiasthmatic; cardiant; anticoagulant; antithrombotic; anti-HIV; virucide; antibacterial; antimigraine; **antiangiogenic**; osteopathic; antiarteriosclerotic; antiulcer; antiallergic; ophthalmological; gynecological; immunostimulant; osteopathic; hepatotropic; nephrotropic; uropathic; antiinfertility; auditory; antiparkinsonian.

MECHANISM OF ACTION - STS inhibitor. The compound 2-chloro-estrone-3-O-sulfamate had an IC50 of 0.8 nM against STS (e.g. using MCF-7 breast cancer cells).

USE - (I) can be used for **treating** a condition or disease associated with STS or in the manufacture of a medicament for use in the **therapy** of a condition or disease associated with adverse STS levels (claimed). They can be used for **treating** cell cycling disorders. They can be used for the **treatment** of cancer and for the control of estrogen levels in the body, e.g. for fertility control, such as an oral contraceptive. They can also be used for enhancing the memory function of patients suffering from illnesses such as amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post-stroke dementia or individuals otherwise seeking memory enhancement. They can also be used to decrease the ability of sensitized T cells to mount a TH1 (high IL-2, IFN, low IL-4) response. They can also be used for **treating** inflammatory

conditions. They can also be used for **treating** dermatological disorders, fever, cardiovascular effects, hemorrhage, coagulation and acute phase response, cachexia, anorexia, acute infection, HIV infection, shock states, graft-versus-host reactions, autoimmune disease, reperfusion injury, meningitis, migraine and aspirin-dependent anti-thrombosis, tumor growth, invasion and spread, **angiogenesis**, metastases, malignant, ascites and malignant pleural effusion, cerebral ischemia, ischemic heart disease, osteoarthritis, rheumatoid **arthritis**, osteoporosis, stroke, vasculitis, periodontitis, gingivitis, **psoriasis**, atopic dermatitis, chronic ulcers, epidermolysis bullosa, corneal ulceration, retinopathy and surgical wound healing, rhinitis, allergic conjunctivitis, anaphylaxis, **restenosis**, congestive heart failure, **endometriosis**, atherosclerosis or endosclerosis, cytokine and **cell proliferation** /differentiation activity, immunosuppressant or immunostimulant activity, regulation of hematopoiesis, promoting growth of bone, cartilage, tendon, ligament and nerve tissue and neurodegeneration, inhibition or activation of follicle-stimulating hormone (modulation of fertility), chemotactic/chemokinetic activity (e.g. for mobilizing specific cell types to sites of injury or infection), hemostatic and thrombolytic activity (e.g. for **treating** hemophilia and stroke), antiinflammatory activity (for **treating** e.g. septic shock or Crohn's disease), as antimicrobials, modulators of e.g. metabolism or behavior, as analgesics, **treating** specific deficiency disorders, in **treatment** of e.g. **psoriasis**, in human or veterinary medicine. They may also be useful in the **treatment** of disorders such as macrophage inhibitory and/or T cell inhibitory activity and thus, anti-inflammatory activity, anti-immune activity, i.e. inhibitory effects against a cellular and/or humoral immune response, including a response not associated with inflammation, inhibit the ability of macrophages and T cells to adhere to extracellular **matrix** components and fibronectin, as well as up-regulated fas receptor expression in T cells, inhibit unwanted immune reaction and inflammation including **arthritis**, including rheumatoid **arthritis**, inflammation associated with hypersensitivity, allergic reactions, asthma, systemic lupus erythematosus, collagen diseases and other autoimmune diseases, inflammation associated with atherosclerosis, arteriosclerosis, atherosclerotic heart disease, reperfusion injury, cardiac arrest, myocardial infarction, vascular inflammatory disorders, respiratory distress syndrome or other cardiopulmonary diseases, inflammation associated with peptic ulcer, hepatic fibrosis, liver cirrhosis or other hepatic diseases, thyroiditis or other glandular diseases, glomerulonephritis or other renal and urologic diseases, otitis or other oto-rhino-laryngological diseases, dermatitis or other dermal diseases, orchitis or epididymo-orchitis, infertility, orchidial trauma or other immune-related testicular diseases, placental dysfunction, placental insufficiency, habitual abortion, eclampsia, pre-eclampsia and other immune and/or inflammatory-related gynecological diseases, posterior uveitis, intermediate uveitis, anterior uveitis, conjunctivitis, chorioretinitis, uveoretinitis, optic neuritis, intraocular inflammation, e.g. retinitis or cystoid macular edema, sympathetic ophthalmia, scleritis, retinitis pigmentosa, immune and inflammatory components of degenerative fundus disease, inflammatory components of ocular trauma, ocular inflammation caused by infection,

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proliferative vitreo-retinopathies, acute ischemic optic neuropathy, excessive scarring, e.g. following glaucoma filtration operation, immune and/or inflammation reaction against ocular **implants** and other immune and inflammatory-related ophthalmic diseases, inflammation associated with autoimmune diseases or conditions or disorders where, both in the central nervous system (CNS) or in any other organ, immune and/or inflammation suppression would be beneficial, Parkinson's disease, complication and/or side effects from **treatment** of Parkinson's disease, AIDS-related dementia complex HIV-related encephalopathy, Devic's disease, Sydenham chorea, Alzheimer's disease and other degenerative diseases and conditions or disorders of the CNS.
Dwg.0/14

L20 ANSWER 2 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-482964 [52] WPIDS
DOC. NO. CPI: C2001-144694
TITLE: New device for **implanting** a cell culture in a host is useful for **implanting** a cell culture in a host, administering a **therapeutic** substance to a host or to **treat** a disease.
DERWENT CLASS: A96 B04 D16 D22
INVENTOR(S): HARPSTEAD, S D
PATENT ASSIGNEE(S): (RSTI-N) RST IMPLANTED CELL TECHNOLOGY LLC
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001043696	A2	20010621	(200152)*	EN	19
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
AU 2001043107	A	20010625	(200162)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001043696	A2	WO 2000-US42628	20001206
AU 2001043107	A	AU 2001-43107	20001206

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001043107	A Based on	WO 200143696

PRIORITY APPLN. INFO: US 1999-464560 19991216
AN 2001-482964 [52] WPIDS
AB WO 200143696 A UPAB: 20010914
NOVELTY - A device (I) for **implanting** a cell culture in a host is new.

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DETAILED DESCRIPTION - (I) comprises:

(1) a biocompatible deformable body comprising a wall defining at least one aperture; and

(2) a biocompatible microporous membrane supported by the deformable body such that the deformable body and microporous membrane define a cavity and the microporous membrane defines an enclosed cavity.

INDEPENDENT CLAIMS are also included for:

(1) **implanting** (M1) a cell culture in a host comprising:

(a) **implanting** a device (Ia) in the host, where the device comprises:

(i) (1) and (2) of (I); and

(ii) a sealable port adapted and configured for adding the cell culture to the cavity; and

(b) placing the cell culture into the cavity of the device;

(2) administering (M2) a **therapeutic** substance to a host comprising:

(a) **implanting** (Ia);

(b) injecting the cell culture into the cavity of the device where the cell culture is capable of producing the **therapeutic** substance; and

(c) permitting the **therapeutic** substance produced by the cell culture to pass into the host; and

(3) **treating** (M3) a disease comprising the steps of (M2).

USE - The invention provides a method for **implanting** a cell culture in a host, administering a **therapeutic** substance to a host or to **treat** a disease.

ADVANTAGE - The invention provides a method which increases the rate of successful **implantation** and increases the long term viability of **implanted** cells.
Dwg.0/2

L20 ANSWER 3 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-389951 [41] WPIDS
DOC. NO. CPI: C2001-118827
TITLE: Bioreactor for systemic delivery of bioactive agents, comprises nucleic acids encoding growth stimulating and bioactive agents, and a biocompatible substance capable of cellular infiltration.
DERWENT CLASS: A14 A17 A28 A89 B04 B07 D16 D22
INVENTOR(S): CHANDLER, L A; PIERCE, G
PATENT ASSIGNEE(S): (SELE-N) SELECTIVE GENETICS INC
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001040272	A2	20010607	(200141)*	EN	69
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC					
MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE					
DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG					
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ					
PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN					
YU ZA ZW					

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AU 2001019398 A 20010612 (200154)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001040272	A2	WO 2000-US32754	20001130
AU 2001019398	A	AU 2001-19398	20001130

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001019398	A Based on	WO 200140272

PRIORITY APPLN. INFO: US 1999-168470P 19991201

AN 2001-389951 [41] WPIDS

AB WO 200140272 A UPAB: 20010724

NOVELTY - An in situ bioreactor (I) adapted for systemic delivery of bioactive agents, comprising a nucleic acid encoding a growth stimulating agent, a nucleic acid encoding a bioactive agent, and a biocompatible substance capable of cellular infiltration, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

- (1) systemic delivery of a protein from a tissue site in an animal, comprising contacting the tissue site with (I);
- (2) a Bi-gene device comprising a biocompatible substance capable of cellular infiltration, a nucleic acid encoding a cell growth stimulating agent, and a second nucleic acid encoding a bioactive agent;
- (3) a kit for the production of a device comprising:
 - (a) a container;
 - (b) a biocompatible substance;
 - (c) a nucleic acid encoding a cell growth stimulating agent;and
 - (d) a second nucleic acid encoding a bioactive agent; and
 - (4) a kit for the production of a coated device comprising:
 - (a) a device coated with a biocompatible substance;
 - (b) a nucleic acid encoding a growth stimulating agent; and
 - (c) a second nucleic acid encoding a bioactive agent.

ACTIVITY - Vulnerary; hemostatic; antianemic; antidiabetic; antiarthritic; coagulant; antiinflammatory; immunosuppressive; neuroprotective; cytostatic; antirheumatic; osteopathic; anti-infertility; contraception.

MECHANISM OF ACTION - Bioactive agent deliverer; protein and gene therapy.

USE - (I) is used for cellular ingrowth and systemic delivery of a bioactive agent, such as a protein from a tissue site in an animal (claimed). (I) is used as an **implant**. (I) can be used to **treat** conditions associated with renal dialysis, hemophilia, hemoglobinopathies, thalassemias, anemia, lipid storage disease, mucopolysaccharidoses, diabetes, hypercoagulability, **arthritis**, hypercoagulability, stroke, cerebroprotective, inflammation, infection, autoimmunity, **multiple sclerosis**, thrombocytopenia, cancer, osteoporosis, infertility, and birth control.

ADVANTAGE - (I) allows sustained and controlled gene delivery as well as sustained product expression using in vivo transfer and

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expression of desired nucleic acids.
Dwg.0/3

L20 ANSWER 4 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2001-529116 [58] WPIDS

CROSS REFERENCE: 1999-443815 [32]

DOC. NO. CPI: C2001-157777

TITLE: **Treating** mammals having disorders associated with pathological **matrix** metalloprotease activity e.g. **arthritis** or tumor invasion, by administering selective aromatic sulfone-hydroxamic acid metalloprotease inhibitors.

DERWENT CLASS: B05

INVENTOR(S): BARTA, T E; BECKER, D P; BOEHM, T L; DECRESCENZO, G A; FRESKOS, J N; GETMAN, D P; HANSON, G J; MCDONALD, J J; WILLAMIL, C I

PATENT ASSIGNEE(S): (BART-I) BARTA T E; (BECK-I) BECKER D P; (BOEH-I) BOEHM T L; (DECR-I) DECRESCENZO G A; (FRES-I) FRESKOS J N; (GETM-I) GETMAN D P; (HANS-I) HANSON G J; (MCDO-I) MCDONALD J J; (WILL-I) WILLAMIL C I

COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2001014688	A1	20010816	(200158)*		423

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2001014688	A1	Provisional	US 1997-66007P 19971114
		Provisional	US 1998-95347P 19980804
		Provisional	US 1998-95501P 19980806
			US 1998-191129 19981113

PRIORITY APPLN. INFO: US 1998-191129 19981113; US 1997-66007P 19971114; US 1998-95347P 19980804; US 1998-95501P 19980806

AN 2001-529116 [58] WPIDS

CR 1999-443815 [32]

AB US2001014688 A UPAB: 20011010

NOVELTY - **Treating** mammals having a disorder associated with **matrix** metalloprotease (MMP) activity by administering an inhibitor (I), or its salt, that inhibits at least one of MMP-2, -9 or -13 but has significantly lower inhibitory activity against MMP-1.

DETAILED DESCRIPTION - **Treating** mammals having a disorder associated with pathological **matrix** metalloprotease (MMP) activity by administering a metalloprotease inhibitor of formula (I), or its salt, that inhibits at least one of MMP-2, -9 or -13 but has significantly lower inhibitory activity against MMP-1,

HO-NH-CO-CR1R2-SO2-R3 (I)

R1, R2 = H; or

R1 + R2 together with atom to which they are bonded = 5 to

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8-membered ring, containing 1-3 O, S or N;

R3 = optionally substituted (hetero)aryl

The full definitions are given in the DEFINITIONS (Full Definitions) Field. INDEPENDENT CLAIMS are also included for the following:

(a) compounds of formula (II) and their salts,

R14 = H, cation or CWR15;

W = O or S;

R15 = substituent;

m, n, p = 0-2, and;

m+n+p = 1-4.

X, Y and Z, individually or in combination, = wide range of atoms or groups;

G-A-R-E-Y = substituent longer than a pentyl group but shorter than icosyl;

(b) intermediates of formula (VI),

R20 = -OR21 or -NHOR22;

R21 = H, 1-6C alkyl (optionally substituted by aryl), aryl or cation;

R22 = selectively removable protecting group; and

g = 0-2;

(c) composition containing (II) dissolved or dispersed in a carrier; and

(d) method for making MMP inhibitors or their intermediates.

ACTIVITY - Antiarthritic; Antiulcer; Antitumor;

Antiangiogenic; Antithrombotic; Anti-inflammatory; Cardiovascular.

Nude mice were **implanted** with 3-5 million PC-3 human cancer cells, then **treated** twice daily, by gavage, with 10 mg/kg/day of N-hydroxy-4-((4-(phenylthio)phenyl) sulfonyl)-1-(2-propynyl)-4-piperidine carboxamide, monohydrochloride of formula (Ia). This **treatment** reduced tumor size (after 25-30 days) by 40%; compare less than 5% reduction for marimastat.

MECHANISM OF ACTION - Inhibition of MMP.

USE - (I) are used to **treat** rheumatoid

arthritis; osseous arthritis; septic **arthritis**; corneal, epidermal or gastric ulcers; metastasis, invasion or **angiogenesis** of tumors; proteinuria; coronary thrombosis and bone disease, also (by inhibiting activity of tumor necrosis factor alpha convertase) the acute phase of shock and sepsis, coagulation, hemorrhage, cardiovascular effects, fever, inflammation, anorexia and cachexia.

ADVANTAGE - Selectivity of (I) minimizes side-effects associated with inhibition of MMP-1. The compound N-hydroxy-4-((4-(phenylthio)phenyl) sulfonyl)-1-(2-propynyl)-4-piperidine carboxamide, monohydrochloride (Ia) had IC50 of 0.5, 0.2, 9000 and 1.5 against MMP-13, -2, -1 and -9, respectively.
Dwg.0/0

L20 ANSWER 5 OF 42

MEDLINE

DUPLICATE 1

ACCESSION NUMBER:

2001520593

MEDLINE

DOCUMENT NUMBER:

21439139

PubMed ID: 11555602

TITLE:

Treatment with low-dose interferon-alpha restores the balance between **matrix**

metalloproteinase-9 and E-cadherin expression in human transitional cell carcinoma of the bladder.

AUTHOR:

Slaton J W; Karashima T; Perrotte P; Inoue K; Kim S J; Izawa J; Kedar D; McConkey D J; Millikan R;

Searcher :

Shears

308-4994

09/822161

CORPORATE SOURCE: Sweeney P; Yoshikawa C; Shuin T; Dinney C P
Department of Cancer Biology, The University of Texas
M. D. Anderson Cancer Center, Houston, Texas 77030,
USA.
CONTRACT NUMBER: 67914 (NCI)
CA 16672
SOURCE: CLINICAL CANCER RESEARCH, (2001 Sep) 7 (9) 2840-53.
Journal code: C2H; 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010925
Last Updated on STN: 20011008
Entered Medline: 20011004

AB Tumor invasion and metastasis are regulated by the expression of genes such as E-cadherin, which regulates cell **adhesion**, and **matrix** metalloproteinase-9 (MMP-9), which alters the integrity of the extracellular **matrix**. Both up-regulation of MMP-9 and down-regulation of E-cadherin correlate with bladder cancer metastasis. The purpose of this study was first to determine whether an imbalance between MMP-9 and E-cadherin expression correlates with metastasis from human transitional cell carcinoma (TCC) of the bladder after **therapy** with neoadjuvant chemotherapy and radical cystectomy and then to determine whether **treatment** of human TCC xenografts growing in nude mice with interferon (IFN)-alpha would restore this balance, thereby limiting tumor invasion and metastasis. We used in situ hybridization to evaluate the expression of several metastasis-related genes, including MMP-9 and E-cadherin, in paraffin-embedded biopsy specimens from 55 patients with muscle-invasive TCC **treated** with neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin chemotherapy and radical cystectomy. By multivariate analysis, an MMP-9:E-cadherin ratio of >1.8 was an independent prognostic factor for disease progression. In vitro incubation of an IFN-resistant, highly metastatic human TCC cell line, 253J B-V(R) with noncytostatic concentrations of IFN-alpha down-regulated the activity of MMP-9, up-regulated E-cadherin, and inhibited in vitro invasion. 253J B-V(R) cells were **implanted** into the bladders of athymic nude mice. Systemic **therapy** with IFN-alpha (10,000 units s.c. daily) decreased the expression of MMP-9, increased expression of E-cadherin, reduced tumor volume, and inhibited metastasis. The MMP-9:E-cadherin ratio was 4.5 in untreated controls and 1.1 after IFN-alpha **treatment**. Moreover, systemic low-dose daily IFN-alpha potentiated the efficacy of paclitaxel. These studies indicate that in addition to its antiproliferative and **antiangiogenic** effects, IFN-alpha limits tumor invasion by restoring the normal balance between MMP-9 and E-cadherin and enhances the activity of systemic chemotherapy.

L20 ANSWER 6 OF 42 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001189682 MEDLINE
DOCUMENT NUMBER: 21174992 PubMed ID: 11280779
TITLE: Angiopoietin-2 is related to tumor
angiogenesis in gastric carcinoma: possible
in vivo regulation via induction of proteases.
AUTHOR: Etoh T; Inoue H; Tanaka S; Barnard G F; Kitano S;

09/822161

Mori M
CORPORATE SOURCE: Department of Surgery, Medical Institute of
Bioregulation, Kyushu University, Beppu, Japan.
SOURCE: CANCER RESEARCH, (2001 Mar 1) 61 (5) 2145-53.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20010425
Entered Medline: 20010419

AB Tumor **angiogenesis** progresses by a dynamic balance between tumor vascular regression and growth. Angiopoietin (Ang)-2 (the natural antagonist for the **angiogenic** Tie-2 receptor) and vascular endothelial growth factor (VEGF) are thought to be critical regulators in this process; therefore, these may play a critical role in cancer aggressiveness. The aim of this study was to clarify the clinical and biological significance of the expression of Ang-2 in human gastric cancers and to investigate the relationship between Ang-2 together with VEGF and the induction of proteases such as **matrix metalloproteinases (MMPs)** in the process of tumor development. Eighty-five individuals with gastric cancer, who had undergone surgery without preoperative **treatment**, were studied. A stable transfectant of the human MKN-7 gastric cancer cell lines with an Ang-2 expression vector was used for the experimental study. First, we examined the relationship between the mRNA expression of Angs by Northern blot analysis and clinicopathological features. High Ang-2-expression cases showed more frequent vascular involvement and more advanced stages of disease compared with low Ang-2-expression cases ($P < 0.05$). With regard to prognosis, the survival time for patients in the high-Ang-2 mRNA group was significantly shorter ($P < 0.05$). When we examined the localization of Ang-2 in human gastric cancers, immunohistochemical analysis revealed that this protein was expressed predominantly in cancer tissues when compared with normal tissues. Interestingly it was expressed not only in endothelia cells (ECs) but also in cancer cells. Second, Ang-2-transfected cells were **implanted** in vivo into the gastric walls of nude mice. Ang-2-transfectant mice developed highly metastatic tumors with hypervascularity as compared with MKN-7 or control vector-transfectant tumors. There was a significant correlation between Ang-2 mRNA expression and lower grade of vessel maturation. Third, on the basis of the in vivo data, we focused on production of proteases such as MMPs to investigate possible mechanisms in these processes. MMP-1, MMP-9, and urokinase-type plasminogen activator in ECs were strongly up-regulated by Ang-2 in the presence of VEGF in vitro. These data suggest that production of Ang-2 is implicated in tumor development in human gastric cancers. Its production may contribute to tumor **angiogenesis** by induction of proteases in ECs, which may be enhanced in the presence of VEGF.

L20 ANSWER 7 OF 42 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001417243 MEDLINE
DOCUMENT NUMBER: 21359557 PubMed ID: 11466388
TITLE: Evidence of IL-18 as a novel **angiogenic** mediator.

Searcher : Shears 308-4994

09/822161

AUTHOR: Park C C; Morel J C; Amin M A; Connors M A; Harlow L A; Koch A E
CORPORATE SOURCE: Department of Medicine, Northwestern University Medical School, 303 East Chicago Avenue, Chicago, IL 60611, USA.
CONTRACT NUMBER: AI 40987 (NIAID)
AR 30692 (NIAMS)
HL 58695 (NHLBI)
SOURCE: JOURNAL OF IMMUNOLOGY, (2001 Aug 1) 167 (3) 1644-53.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011029
Last Updated on STN: 20011029
Entered Medline: 20011025

AB **Angiogenesis**, or new blood vessel growth, is a key process in the development of synovial inflammation in rheumatoid arthritis (RA). Integral to this pathologic proliferation are proinflammatory cytokines. We hypothesized a role for IL-18 as an **angiogenic** mediator in RA. We examined the effect of human IL-18 on human microvascular endothelial cell (HMVEC) migration. IL-18 induced HMVEC migration at 1 nM ($p < 0.05$). RA synovial fluids potently induced endothelial cell migration, but IL-18 immunodepletion resulted in a 68 +/- 5% decrease in HMVEC migration ($p < 0.05$). IL-18 appears to act on HMVECs via $\alpha(v)\beta(3)$ integrin. To test whether IL-18 induced endothelial cell tube formation in vitro, we quantitated the degree of tube formation on Matrigel **matrix**. IL-18, 1 or 10 nM, resulted in a 77% or 87% increase in tube formation compared with control ($p < 0.05$). To determine whether IL-18 may be **angiogenic** in vivo, we **implanted** IL-18 in Matrigel plugs in mice, and IL-18 at 1 and 10 nM induced **angiogenesis** ($p < 0.05$). The **angiogenesis** observed appears to be independent of the contribution of local TNF- α , as evidenced by adding neutralizing anti-TNF- α Ab to the Matrigel plugs. In an alternative in vivo model, sponges embedded with IL-18 or control were **implanted** into mice. IL-18 (10 nM) induced a 4-fold increase in **angiogenesis** vs the control ($p < 0.05$). These findings support a novel function for IL-18 as an **angiogenic** factor in RA and may elucidate a potential **therapeutic** target for **angiogenesis**-directed diseases.

L20 ANSWER 8 OF 42 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 4
ACCESSION NUMBER: 2001311737 EMBASE
TITLE: Molecular properties and involvement of heparanase in cancer progression and normal development.
AUTHOR: Vlodavsky I.; Goldshmidt O.; Zcharia E.; Metzger S.; Chajek-Shaul T.; Atzmon R.; Guatta-Rangini Z.; Friedmann Y.
CORPORATE SOURCE: I. Vlodavsky, Department of Oncology, Hadassah-Hebrew University Hospital, POB 12000, Jerusalem 91120, Israel. vlodavsk@cc.huji.ac.il
SOURCE: Biochimie, (2001) 83/8 (831-839).
Refs: 38

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ISSN: 0300-9084 CODEN: BICMBE
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
030 Pharmacology
029 Clinical Biochemistry
022 Human Genetics
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Heparan sulfate proteoglycans (HSPGs) play a key role in the self-assembly, insolubility and barrier properties of basement membranes and extracellular matrices. Hence, cleavage of heparan sulfate (HS) affects the integrity and functional state of tissues and thereby fundamental normal and pathological phenomena involving cell migration and response to changes in the extracellular microenvironment. Here, we describe the molecular properties, expression and function of a human heparanase, degrading HS at specific intrachain sites. The enzyme is synthesized as a latent .apprx.65 kDa protein that is processed at the N-terminus into a highly active .apprx.50 kDa form. The heparanase mRNA and protein are preferentially expressed in metastatic cell lines and human tumor tissues. Overexpression of the heparanase cDNA in low-metastatic tumor cells conferred a high metastatic potential in experimental animals, resulting in an increased rate of mortality. The heparanase enzyme also releases ECM-resident **angiogenic** factors in vitro and its overexpression induces an **angiogenic** response in vivo. Heparanase may thus facilitate both tumor cell invasion and neovascularization, both critical steps in cancer progression. The enzyme is also involved in cell migration associated with inflammation and autoimmunity. The unexpected identification of a single predominant functional heparanase suggests that the enzyme is a promising target for drug development. In fact, **treatment** with heparanase inhibitors markedly reduces tumor growth, metastasis and autoimmune disorders in animal models. Studies are underway to elucidate the involvement of heparanase in normal processes such as **implantation**, embryonic development, morphogenesis, tissue repair, inflammation and HSPG turnover. Heparanase is the first functional mammalian HS-degrading enzyme that has been cloned, expressed and characterized. This may lead to identification and cloning of other glycosaminoglycan degrading enzymes, toward a better understanding of their involvement and significance in normal and pathological processes. .COPYRG. 2001 Societe francaise de biochimie et biologie moleculaire / Editions scientifiques et medicales Elsevier SAS. All rights reserved.

L20 ANSWER 9 OF 42 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001327142 EMBASE

TITLE: [The role of vasculo-and **angiogenesis** in embryonic and fetal development. A short review].
DIE ROLLE DER VASKULO- UND **ANGIOGENESE** IN DER EMBRYONALEN UND FETALEN ENTWICKLUNG. EINE KURZE UBERSICHT.

AUTHOR: Zygmunt M.; Munstedt K.; Lang U.

CORPORATE SOURCE: Dr. M. Zygmunt, Zentrum Frauenheilkunde/Geburtshilfe, Universitätsfrauenklinik, Klinikstrasse 32, 35385

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Giessen, Germany. marek.zygmunt@gyn.med.uni-giessen.de
SOURCE: Gynakologe, (2001) 34/9 (812-819).
Refs: 88
ISSN: 0017-5994 CODEN: GYNKAP
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
010 Obstetrics and Gynecology
LANGUAGE: German
SUMMARY LANGUAGE: English; German

AB The investigation of the mechanisms regulating the development of new vessels is crucial to our understanding of both tumor biology and the early development of pregnancy. There are striking similarities between tumor invasion and vascularization on the one hand and blastocyst **implantation** and placental development on the other. Both sets of events share two important features: migration and invasion through the extracellular **matrix** and the ability to access the host vascular system and recruit blood supply. Despite these common features, at least two major differences occur. First, invasion and new vessel formation during pregnancy is self-limited compared to the uncontrolled tumor growth and vessel formation during oncogenesis. Second, the **implanting** embryo not only accesses the maternal vascular system, but also forms its own vascular system. Our understanding of the different molecular and functional aspects of these two processes, in particular the self-limitation of trophoblastic invasion and vessel formation during gestation, might allow the development of new **therapeutic** strategies for the **treatment** of both tumors and tumor and pregnancy related pathology. This short review provides a general overview of the recent work on vascular development during early pregnancy and its role in the pathogenesis of pregnancy related disorders.

L20 ANSWER 10 OF 42 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001266170 EMBASE

TITLE: **Matrix** immobilization enhances the tissue repair activity of growth factor gene **therapy** vectors.

AUTHOR: Doukas J.; Chandler L.A.; Gonzalez A.M.; Gu D.; Hoganson D.K.; Ma C.; Nguyen T.; Printz M.A.; Nesbit M.; Herlyn M.; Crombleholme T.M.; Aukerman S.L.; Sosnowski B.A.; Pierce G.F.

CORPORATE SOURCE: Dr. J. Doukas, Selective Genetics, Inc., 11035 Roselle Street, San Diego, CA 92121, United States. jdoukas@selectivegenetics.com

SOURCE: Human Gene Therapy, (2001) 12/7 (783-798).
Refs: 46

ISSN: 1043-0342 CODEN: HGTHE3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 022 Human Genetics
030 Pharmacology
037 Drug Literature Index
039 Pharmacy

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Although growth factor proteins display potent tissue repair

activities, difficulty in sustaining localized **therapeutic** concentrations limits their **therapeutic** activity. We reasoned that enhanced histogenesis might be achieved by combining growth factor genes with biocompatible **matrices** capable of immobilizing vectors at delivery sites. When delivered to subcutaneously **implanted** sponges, a platelet-derived growth factor B-encoding adenovirus (AdPDGF-B) formulated in a collagen **matrix** enhanced granulation tissue deposition 3- to 4-fold ($p < 0.0002$), whereas vectors encoding fibroblast growth factor 2 or vascular endothelial growth factor promoted primarily **angiogenic** responses. By day 8 posttreatment of ischemic excisional wounds, collagen-formulated AdPDGF-B enhanced granulation tissue and epithelial areas up to 13- and 6-fold ($p < 0.009$), respectively, and wound closure up to 2-fold ($p < 0.05$). At longer times, complete healing without excessive scar formation was achieved. Collagen **matrices** were shown to retain both vector and transgene products within delivery sites, enabling the transduction and stimulation of infiltrating repair cells. Quantitative PCR and RT-PCR demonstrated both vector DNA and transgene mRNA within wound beds as late as 28 days posttreatment. By contrast, aqueous formulations allowed vector seepage from application sites, leading to PDGF-induced hyperplasia in surrounding tissues but not wound beds. Finally, repeated applications of PDGF-BB protein were required for neotissue induction approaching equivalence to a single application of collagen-immobilized AdPDGF-B, confirming the utility of this gene transfer approach. Overall, these studies demonstrate that immobilizing **matrices** enable the controlled delivery and activity of tissue promoting genes for the effective regeneration of injured tissues.

L20 ANSWER 11 OF 42 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 5
 ACCESSION NUMBER: 2001:302527 BIOSIS
 DOCUMENT NUMBER: PREV200100302527
 TITLE: Long- and short-term effects of biological hydrogels on capsule microvascular density around **implants** in rats.
 AUTHOR(S): Ravin, A. G.; Olbrich, K. C.; Levin, L. S.; Usala, A.-L.; Klitzman, B. (1)
 CORPORATE SOURCE: (1) Kenan Plastic Surgery Research Labs, Duke University Medical Center, Durham, NC, 27710: klitz@duke.edu USA
 SOURCE: Journal of Biomedical Materials Research, (2001) Vol. 58, No. 3, pp. 313-318. print.
 ISSN: 0021-9304.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB Fibrous capsule formation around **implants** can inhibit solute exchange between **implantable** devices and the circulation. Parylene-n coated polycarbonate disks surrounded with growth factor reduced Matrigel(R) (MG) or several gelatin-based **matrices** were **implanted** intramuscularly into rats for 21 or 50 days. MG supplemented with vascular endothelial growth factor (VEGF) or basic fibroblast growth factor (bFGF) increased capsule microvascular density at 21 days ($p < 0.05$) when compared to bare parylene-coated polycarbonate disks (control). The increased microvascular density around VEGF- and bFGF-**treated**

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implants regressed by 50 days and was no longer significantly different from controls. The microvascular density induced by the gelatin-based **matrices** was not significantly different from controls at 21 days, but was increased at 50 days ($p < 0.05$), suggesting a slower, long-term effect. Disks **treated** with MG and gelatin-based **matrices** had thinner capsules at 21 days ($p < 0.05$). By 50 days, the capsule thicknesses around these **implants** were no longer statistically thinner than controls. The capsule thickness around **implants treated** with VEGF, bFGF, and essential gelatin-based **matrix** was thinner than controls at 50 days ($p < 0.05$). These results indicate that it is possible to increase functional microvascular density within fibrous capsules using **angiogenic** growth factors and gelatin-based **matrices**. However, this effect may be short-lived, requiring chronic administration of growth factors.

L20 ANSWER 12 OF 42 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2001119511 MEDLINE
DOCUMENT NUMBER: 21072616 PubMed ID: 11204275
TITLE: Fibroblast growth factor 2 activation of stromal cell
vascular endothelial growth factor expression and
angiogenesis.
AUTHOR: Claffey K P; Abrams K; Shih S C; Brown L F; Mullen A;
Keough M
CORPORATE SOURCE: Department of Physiology, University of Connecticut
Health Center, Farmington 06030, USA..
claffey@sun.uhc.edu
CONTRACT NUMBER: CA-64436 (NCI)
SOURCE: LABORATORY INVESTIGATION, (2001 Jan) 81 (1) 61-75.
Journal code: KZ4. ISSN: 0023-6837.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010215

AB **Angiogenesis** is a key component of human cancer progression and metastasis. In an effort to recapitulate early events in tumor-induced **angiogenesis**, we have employed a subcutaneous Matrigel **implant** model using immunodeficient mice as hosts. Matrigel-containing fibroblast growth factor 2 (FGF-2; 1.2 microg/ml) induced stromal cell infiltration into the Matrigel/skin interface within 4 days and maximal neovascularization at 7 days. Cells staining positive for the endothelial cell marker, platelet-endothelial cell **adhesion** molecule 1 (PECAM-1), were present in neovessels and in isolated cells within the Matrigel **matrix**. Immunohistochemical analysis revealed high levels of vascular endothelial growth factor (VEGF) deposited in the stromal interface present only in the FGF-2-containing but not in control Matrigel **implants**. VEGF expression was confirmed with in situ hybridization. High VEGF mRNA levels were observed in the infiltrating stromal cells but not in endothelial or endothelial precursors as defined by PECAM-1 staining. In vitro analysis of FGF-2-**treated** embryonic fibroblasts, Balb/c 3T3 cells, showed an induction of VEGF transcription, mRNA synthesis, and

protein secretion as defined by transcriptional reporter, Northern blot, and ELISA assays. The FGF-2-induced VEGF expression was not dependent on select **matrix** adherence or signaling components because VEGF mRNA expression induced by FGF-2 was equally activated on serum, basement membrane, and fibronectin **matrix** substrates. Systemic application of anti-VEGF antibodies significantly repressed FGF-2-induced **angiogenesis** over control antibody by 88% ($p < 0.001$). These data support an FGF-2 **angiogenic** model that is dependent on endothelial cell activation, stromal cell infiltration, and VEGF expression by the infiltrating stromal cell population.

L20 ANSWER 13 OF 42 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001036407 EMBASE

TITLE: Social isolation stress augments **angiogenesis** induced by colon 26-L5 carcinoma cells in mice.

AUTHOR: Wu W.; Murata J.; Murakami K.; Yamaura T.; Hayashi K.; Saiki I.

CORPORATE SOURCE: Prof. I. Saiki, Institute of Natural Medicine, Toyama Med./Pharmaceutical Univ., 2630 Sugitani, Toyama 930-0194, Japan. byosei@ms.toyama-mpu.ac.jp

SOURCE: Clinical and Experimental Metastasis, (2001) 18/1 (1-10).

Refs: 44

ISSN: 0262-0898 CODEN: CEXMD2

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer

LANGUAGE: English

SUMMARY LANGUAGE: English

AB We have previously shown that tumor necrosis factor-.alpha. (TNF-.alpha.), which is an important **angiogenesis**-related factor, was over-secreted in male BALB/c mice under social isolation stress as compared with the control, and closely associated with a remarkable elevation of tumor invasion and metastasis of colon 26-L5 carcinoma cells. In the present study, we explored the effect of isolation stress on the **angiogenesis** caused by colon 26-L5 carcinoma cells in vivo and in vitro. Social isolation lead to the enhancement of tumor growth after intrahepatic **implantation** with a fragment of colon 26-L5 tumor. **Angiogenic** response (number of vessels oriented towards tumor mass) and tumor growth (size) were significantly increased in the socially isolated mouse relative to that in the group-housed mice. Furthermore, higher protein level of hepatic TNF-.alpha. was found in the stressed mice than that in the control. Expression of mRNA for vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) were also elevated in the tumor regions and liver tissues of the stressed mice in comparison with that in group-housed mice. On the other hand, hepatic sinusoidal endothelial (HSE) cells **treated** with TNF-.alpha. exhibited a marked promotion of the migration, invasion, expression of mRNA for **matrix** metalloproteinase (MMP)-9, and tube-like formation, but no cytotoxicity against the cells in vitro. The above data suggest that the social isolation stress augmented the tumor-induced **angiogenesis** probably by up-regulating the **angiogenesis**-related factors, including TNF-.alpha., VEGF and HGF, and consequently mediating the functions of endothelial

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cells such as migration, invasion, and tube-like formation.

L20 ANSWER 14 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-025136 [03] WPIDS
DOC. NO. CPI: C2001-007749
TITLE: METH1 and METH2 polynucleotides and encoded
polypeptides, used to inhibit angiogenesis in the
treatment of disorders such as cancer,
rheumatoid **arthritis** and
psoriasis.
DERWENT CLASS: B04 D16
INVENTOR(S): FORNWALD, J A; HASTINGS, G A; IRUELA-ARISPE, L;
JONAK, Z L; RUBEN, S M; TERRETT, J A; TRULLI, S H
PATENT ASSIGNEE(S): (BETH-N) BETH ISRAEL DEACONESS MEDICAL CENT;
(FORN-I) FORNWALD J A; (HAST-I) HASTINGS G A;
(HUMA-N) HUMAN GENOME SCI INC; (IRUE-I)
IRUELA-ARISPE L; (JONA-I) JONAK Z L; (RUBE-I) RUBEN
S M; (SMIK) SMITHKLINE BEECHAM CORP; (TERR-I)
TERRETT J A; (TRUL-I) TRULLI S H
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000071577	A1	20001130	(200103)*	EN	764
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC					
MW MZ NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK					
DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP					
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL					
PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU					
ZA ZW					
AU 2000050459	A	20001212	(200115)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000071577	A1	WO 2000-US14462	20000525
AU 2000050459	A	AU 2000-50459	20000525

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000050459	A Based on	WO 200071577

PRIORITY APPLN. INFO: US 2000-183792P 20000222; US 1999-318208
19990525; US 1999-144882P 19990720; US
1999-147823P 19990810; US 1999-373658
19990813; US 1999-171503P 19991222

AN 2001-025136 [03] WPIDS
AB WO 200071577 A UPAB: 20010116
NOVELTY - An isolated nucleic acid (I) encoding residues 1, 2, 29,
or 30-950, 235-459, 460-544, 545-598, 841-894, 895-934, 536-613, or
549-563 of a 950 amino acid sequence (S1) corresponding to METH1, a
968 residue amino acid sequence, or a mature or complete protein
sequence encoded by the cDNA clone contained in ATCC 209581, is new.

Both sequences fully defined in the specification.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

- (1) an isolated nucleic acid (II) encoding residues 1, 2, 24 or 112-890, 440-529, 530-583, 837-890, 280-606 or 529-548 of an 890 amino acid sequence (S2) corresponding to METH2, fully defined in the specification, or the mature or complete amino acid sequence encoded by the cDNA clone contained in ATCC 209582;
- (2) making a recombinant vector comprising inserting (I) or (II) into a vector in operable linkage to a promoter;
- (3) a recombinant vector produced by the method of (2);
- (4) producing a host cell, comprising introducing the vector of (3) into a host cell;
- (5) a host cell produced by the method of (4);
- (6) producing a polypeptide comprising culturing the host cell of (5) under expression conditions;
- (7) an isolated nucleic acid molecule, comprising 50 contiguous nucleotides of a 3261 nucleotide sequence fully defined in the specification, which does not comprise one of 28 127-42521 nucleotide expressed sequence tag sequences, fully defined in the specification;
- (8) an isolated nucleic acid comprising 50 contiguous nucleotides of a 3008 nucleotide sequence, fully defined in the specification, which does not comprise one of 31 88-9248 nucleotide expressed sequence tag sequences, fully defined in the specification;
- (9) an isolated polypeptide encoded by (I) or (II); and
- (10) a polypeptide comprising m-n of (S1) or (S2), where m is 1-890 and n is 10-890.

ACTIVITY - Cytostatic; ophthalmological; antirheumatic; antiarthritic; antipsoriatic; vulnerary; gynecological; dermatological; cardiant; vasotropic; hemostatic; antiinflammatory; antiarteriosclerotic; contraceptive.

MECHANISM OF ACTION - Angiogenesis inhibitor; gene therapy.

Swiss Webster female and male mice were purchased from Charles River and used between 8-10 weeks-old for the **implantation** of pellets containing METH1. Corena pockets were performed as described by Kenyon et al Invest. Ophthalmol. Vis. Sci. 37:1625-1632 (1996) with few modifications. Briefly, a solution of 10 micro g of recombinant vascular endothelial growth factor plus 5 mg sucralfate were mixed with 10 micro l Hydron (RTM) (200 mg/ml in ethanol) and the METH1 (2 micro g). The suspension was smeared onto a sterile nylon mesh square and allowed to dry for 30 minutes. The fibers of the mesh were pulled to produce pellets of 500 cubic micro m that were stored at -20 deg. C. Uniformly sized pellets were selected under a microscope and used for the assays. Mice were anesthetized with Avertin (RTM). An incision was made in the cornea using a Nikon SMZ-U dissecting microscope with the aid of a surgical blade. A single-pellet was **implanted** into the pocket. Five days after pellet **implantation**, corneal **angiogenesis** was evaluated and photographed. The number of vessels that grow within a **matrix** polymer containing the **angiogenic** growth factor was measured. In mice administered the METH1 protein the **angiogenic** response was 25 % of that of control mice.

USE - For inhibiting **angiogenesis** in an individual, and for **treating** cancer, benign tumors, an ocular **angiogenic** disease, rheumatoid arthritis;

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psoriasis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars, nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber syndrome, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma, fibromuscular dysplasia, wound granulation, Crohn's disease or atherosclerosis. The proteins can also be used in birth control. (All claimed). The proteins can also be used in diagnostic methods for the prognosis of cancer. The polypeptides are useful as molecular weight markers on sodium dodecyl sulfate polyacrylamide gel electrophoresis gels or on molecular sieve gel filtration columns.
Dwg.0/11

L20 ANSWER 15 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-040983 [05] WPIDS
DOC. NO. CPI: C2001-011883
TITLE: Composition comprising conditioned cell culture medium for wound healing.
DERWENT CLASS: B04 D13 D16 D21 D22
INVENTOR(S): APPLEGATE, M A; HORWITZ, D L; KERN, A; LANDEEN, L K; MANSBRIDGE, J N; NAUGHTON, G K; PINNEY, R E; RATCLIFFE, A; ZELTINGER, J
PATENT ASSIGNEE(S): (ADTI-N) ADVANCED TISSUE SCI INC
COUNTRY COUNT: 92
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000069449	A2	20001123	(200105)*	EN	67
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000048430	A	20001205	(200113)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000069449	A2	WO 2000-US13016	20000512
AU 2000048430	A	AU 2000-48430	20000512

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000048430	A Based on	WO 200069449

PRIORITY APPLN. INFO: US 1999-313538 19990514
AN 2001-040983 [05] WPIDS
AB WO 200069449 A UPAB: 20010124
NOVELTY - A composition comprising conditioned cell culture medium

which has previously supported the growth of eukaryotic cells cultured in three-dimensions, and a carrier, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a food substance with enhanced nutritional content comprising conditioned cell culture medium, together with a separate food item for consumption by a mammal;

(2) a nutritional supplement comprising conditioned cell culture medium, and a liquid, tablet or capsule carrier for human consumption;

(3) preparing a pharmaceutical composition comprising:

(a) culturing eukaryotic cells in 3-dimensions in a cell culture medium to grow the cells in vitro;

(b) culturing the cells in vitro until the cell culture medium contains a desired level of extracellular products so that a conditioned medium is formed;

(c) removing the conditioned medium from the cells used to condition the medium; and

(d) combining the conditioned medium with a carrier;

(4) improving wound or burn healing comprising administering the novel composition together with a separate **therapeutic** component to reduce the amount of traumatized tissue or scar tissue and improve regeneration of healthy tissue at the wound site;

(5) correction of a cosmetic defect comprising administering the novel composition together with a component useful for cosmetic purposes so that the person exhibits a cosmetic improvement;

(6) inhibiting or reversing the deleterious effects to cells induced by intracellular oxidation in a person comprising administering the novel conditioned cell medium;

(7) stimulating hair growth comprising topical administration of the novel composition together with a topical carrier;

(8) isolating collagen comprising:

(a) precipitating procollagen from medium conditioned by 3-dimensional culture at high salt conditions under neutral pH conditions;

(b) removing the propeptides under acidic conditions so that the triple helix of the collagen remains intact; and

(c) precipitating the collagen at high salt concentrations.

ACTIVITY - Vulnerary.

No biological data is given.

MECHANISM OF ACTION - None given.

USE - For wound and burn healing, particularly of vascular wounds or wounds to the brain, spinal cord, skin, liver, kidney, pancreas, intestines, spleen, genitourinary tract, bone, bone marrow or mucosal tissue, or for inhibiting or reversing the deleterious effects to cells induced by intracellular oxidation, preferably appearance of aging skin. The methods are also useful for stimulating hair growth. The conditioned cell medium can be processed for uses including wound applications, cosmetic additives, food supplements, animal feed supplements, culturing cells, pharmaceutical applications and for stimulating hair growth.

DESCRIPTION OF DRAWING(S) - The figure shows the relative **proliferation** of human **fibroblasts** and **keratinocytes** exposed to conditioned medium (cell culture medium which has previously supported the growth of cells in Transcyte (RTM)). An increase in cell response in as little as 3 days.
Dwg. 3/5

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L20 ANSWER 16 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-611790 [58] WPIDS
DOC. NO. CPI: C2000-183139
TITLE: **Implantable** cell culture device is used
for secreting a growth factor into a target region
of a host e.g. ciliary neurotrophic factor into the
eye to **treat** retinal degradation.
DERWENT CLASS: B04 D16
INVENTOR(S): DEAN, B J; GODDARD, M B I; REIN, D H; STABILA, P F;
TAO, W
PATENT ASSIGNEE(S): (NEUR-N) NEUROTECH SA
COUNTRY COUNT: 92
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000060051	A2	20001012	(200058)*	EN	44
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC					
MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK					
DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP					
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT					
RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA					
ZW					
AU 2000043319	A	20001023	(200107)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000060051	A2	WO 2000-US9150	20000406
AU 2000043319	A	AU 2000-43319	20000406

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000043319	A Based on	WO 200060051

PRIORITY APPLN. INFO: US 2000-543119 20000405; US 1999-127926P
19990406

AN 2000-611790 [58] WPIDS
AB WO 200060051 A UPAB: 20010421
NOVELTY - New **implantable** cell culture device comprises a
semipermeable membrane which permits the diffusion of a growth
factor through it and at least one ARPE-19 cell disposed within the
semipermeable membrane.
ACTIVITY - Antidiabetic; ophthalmological; antiasthmatic;
cytostatic; nootropic; neuroprotective; anticonvulsant;
antiparkinsonian.
No biological data is given.
MECHANISM OF ACTION - None given.
USE - The device is used for delivering a desired factor e.g.
neurotrophin, interleukin, cytokine, anti-apoptotic,
angiogenic, and anti-**angiogenic** factors and
antigens to a recipient host by encapsulating the ARPE-19 cell in
the membrane and **implanting** the device in the target
region e.g. central nervous system, eye, subcutaneous site or

intraperitoneal site (claimed). The desired factor is a **therapeutic** protein, brain derived neurotrophic factor (BDNF), NT-4, ciliary neurotrophic factor (CNTF), Axokine, basic fibroblast growth factor (bFGF), IGF 1, IGF 2, transforming growth factor (TGF) β 2, Midkine, interleukin (IL)-1 β , tumor necrosis factor (TNF), nerve growth factor (NGF), IL-2/3, ILF, IL-6, NTN, Neublastin, vascular endothelial growth factor (VEGF), glial cell derived neurotrophic factor (GDNF), platelet derived growth factor (PDGF), LEDGF, PEDF, antigenic factor or antibody, a gene transfer vector. The desired factor is a **therapeutic** factor used for **treating** cancer and cancer related disorders, cardio-vascular diseases, asthma, metabolic diseases and other relevant pathologies. The factor is delivered to a host with a degenerative disease e.g. Parkinson's Disease, Huntingdon's Disease, ALS, Alzheimer's Disease, Spinal cord injury, Retinopathy of Prematurity, Diabetic Retinopathy, Age-related macular degeneration, Glaucoma, Retinitis pigmentosa, Cataract formation, Retinoblastoma and Retinal ischemia.

ADVANTAGE - Transplantation of cells genetically engineered to produce growth factors by-passes the blood brain barrier and delivers the **therapeutic** factors directly to the target site. Encapsulating the cells in semipermeable membranes protects the cells from acute host immune rejection, reduces the risk of tumor development and reduces the incidences of infection as only a single penetration into the target site is required for continuous growth factor delivery.

ARPE-19 cells have a relatively long life span and good in vivo device viability.

Dwg.0/3

L20 ANSWER 17 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
 ACCESSION NUMBER: 2000-543578 [49] WPIDS
 DOC. NO. CPI: C2000-161800
 TITLE: New human nucleic acids encoding secreted proteins, useful in the **treatment**, prevention or diagnosis of immune disorders (e.g. autoimmune diseases), blood protein disorders and hyperproliferative diseases (e.g. Gaucher's disease).
 DERWENT CLASS: B04 D16
 INVENTOR(S): EBNER, R; FLORENCE, K A; KOMATSOULIS, G; LAFLEUR, D W; MOORE, P A; NI, J; OLSEN, H S; ROSEN, C A; RUBEN, S M; SHI, Y; SOPPET, D R; YOUNG, P E
 PATENT ASSIGNEE(S): (HUMA-N) HUMAN GENOME SCI INC
 COUNTRY COUNT: 87
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000047602	A1	20000817	(200049)*	EN	
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC					
MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES					
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK					
LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG					
SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
AU 2000027575	A	20000829	(200062)		

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APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000047602	A1	WO 2000-US3062	20000208
AU 2000027575	A	AU 2000-27575	20000208

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000027575	A Based on	WO 200047602

PRIORITY APPLN. INFO: US 1999-119468P 19990210

AN 2000-543578 [49] WPIDS

AB WO 200047602 A UPAB: 20001006

NOVELTY - Thirty three human nucleic acids encoding secreted proteins, are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid molecule comprising a nucleotide sequence at least 95% identical to a sequence selected from:

(a) a polynucleotide fragment (N1, sequence defined in the specification), or a polynucleotide fragment of the cDNA sequence (N2) included in an ATCC deposit (various deposit numbers given in the specification) which is hybridizable to N1;

(b) a polynucleotide encoding a polypeptide fragment of an amino acid sequence (P1) defined in the specification, or a polypeptide fragment encoded by N2;

(c) a polynucleotide encoding a polypeptide domain of P1 or a polypeptide domain encoded by N2;

(d) a polynucleotide encoding an epitope of P1 or an epitope encoded by N2;

(e) a polynucleotide encoding P1 or N2, where P1 has biological activity;

(f) a polynucleotide which is a variant, preferably allelic variant, of N1;

(g) a polynucleotide which encodes a species homologue of P1; or

(h) a polynucleotide capable of hybridizing under stringent conditions to any of the polynucleotides of (a) to (g), where the polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a sequence of only A or T residues;

(2) a recombinant vector comprising the nucleic acid molecule of (1);

(3) a method of making a recombinant host cell comprising the nucleic acid molecule of (1);

(4) a recombinant host cell produced by the method of (3);

(5) an isolated polypeptide comprising an amino acid sequence at least 95 % identical to a sequence selected from:

(a) a polypeptide fragment of P1 or the encoded sequence included in an ATCC Deposit (various deposit numbers given in the specification), optionally having biological activity;

(b) a polypeptide domain, epitope, secreted form or full length protein of P1 or the encoded sequence included in ATCC Deposit (various deposit numbers given in the specification);

(c) a variant, preferably allelic variant, of P1; or

(d) a species homologue of P1;

- (6) an isolated antibody that binds specifically to the polypeptide of (5);
- (7) a recombinant host cell that expresses the polypeptide of (5);
- (8) a method of making an isolated polypeptide comprising culturing the recombinant host cell of (7);
- (9) a polypeptide produced by the method of (8);
- (10) a method for preventing, **treating**, or ameliorating a medical condition, comprising administering a **therapeutically** amount of the polypeptide of (5) or the polynucleotide of (1);
- (11) a method of diagnosing a pathological condition or a susceptibility to a pathological condition, comprising:
 - (a) determining the presence or absence of a mutation in the polynucleotide of (1); and
 - (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of the mutation;
- (12) a method of diagnosing a pathological condition or a susceptibility to a pathological condition, comprising:
 - (a) determining the presence or amount of expression of the polypeptide of (5) in a biological sample; and
 - (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide;
- (13) a method for identifying a binding partner to the polypeptide of (5), comprising:
 - (a) contacting the polypeptide of (5) with a binding partner; and
 - (b) determining whether the binding partner effects an activity of the polypeptide.
- (14) a gene corresponding to the cDNA sequence encoding P1;
- (15) a method of identifying an activity in a biological assay, comprising:
 - (a) expressing N1 in a cell;
 - (b) isolating the supernatant;
 - (c) detecting an activity in a biological assay; and
 - (d) identifying the protein in the supernatant having the activity; and
- (16) a product produced by the method of (13).

ACTIVITY - Cytostatic; immunostimulant; antiproliferative; cardiant; antiarrhythmic; antiviral, antibacterial, antifungal, antiparasitic; neuroprotective; nootropic; antiinflammatory; antiangiogenic; anti-HIV; antiarteriosclerotic.

In vivo angiogenesis assay of a polypeptide (S1) defined in the specification measures the ability of an existing capillary network to form new vessels in an implanted capsule of murine extracellular matrix material (Matrigel). Matrigel was purchased from Becton Dickinson Labware/Collaborative Biomedical Products. When thawed at 4 degrees Centigrade, the Matrigel material was a liquid. The Matrigel was mixed with S1 at 150 ng/ml at 4 degrees Centigrade and drawn into cold 3 ml syringes. Female C57Bl/6 mice approximately 8 weeks old were injected with the mixture of Matrigel and experimental protein at 2 sites at the midventral aspect of the abdomen (0.5 ml/site). After 7 days, the mice are sacrificed by cervical dislocation, the Matrigel plugs are removed and cleaned (i.e., all clinging membranes and fibrous tissue was removed). Replicate whole plugs were fixed in neutral buffered 10%

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formaldehyde, embedded in paraffin and used to produce sections for histological examination after staining with Masson's Trichrome. Cross sections from 3 different regions of each plug were processed. Selected sections were stained for the presence of vWF.

The positive control for this assay was bovine basic fibroblast growth factor (FGF) (150 ng/ml). Matrigel alone was used to determine basal levels of angiogenesis. No data was provided.

MECHANISM OF ACTION - None given.

USE - The polynucleotides and polypeptide, or their agonists and antagonists, can be used for treating, preventing or diagnosing immune disorders (e.g. cancer, autoimmune diseases), disorders of hematopoietic cells, blood protein disorders (e.g. agammaglobulinemia), hyperproliferative diseases (e.g. Gaucher's disease), cardiovascular disorders (e.g. congenital heart defects, pulmonary atresia, arrhythmias, ischemia), angiogenesis related disorders (e.g. Crohn's disease, atherosclerosis), neurological diseases (e.g. Alzheimers disease, Huntington's chorea), infectious diseases (e.g. AIDS, cat-scratch disease and other bacterial, viral, parasitic or fungal diseases).

Dwg.0/485

L20 ANSWER 18 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-365610 [31] WPIDS
DOC. NO. NON-CPI: N2000-273559
DOC. NO. CPI: C2000-110472
TITLE: Antibody modulation of claudin-mediated cell
adhesion for increasing vasopermeability,
for delivering drugs to tumors and the nervous
system and across the skin.
DERWENT CLASS: B04 B07 D16 S03
INVENTOR(S): BLASCHUCK, O W; GOUR, B J; SYMONDS, J M
PATENT ASSIGNEE(S): (ADHE-N) ADHEREX TECHNOLOGIES INC
COUNTRY COUNT: 91
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

WO 2000026360	A1	20000511	(200031)*	EN	117
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC					
MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM					
EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ					
LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU					
SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000010223	A	20000522	(200040)		
EP 1127119	A1	20010829	(200150)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK					
NL PT RO SE SI					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

WO 2000026360	A1	WO 1999-CA1029	19991103
AU 2000010223	A	AU 2000-10223	19991103
EP 1127119	A1	EP 1999-953468	19991103
		WO 1999-CA1029	19991103

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000010223	A Based on	WO 200026360
EP 1127119	A1 Based on	WO 200026360

PRIORITY APPLN. INFO: US 1999-282029 19990330; US 1998-185908
19981103

AN 2000-365610 [31] WPIDS

AB WO 200026360 A UPAB: 20000630

NOVELTY - Polypeptide agents (I) (especially antibodies) comprising claudin cell **adhesion** recognition (CAR) sequences and capable of modulating claudin-mediated cell **adhesion**, are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

- (1) a cell **adhesion** modulating agent (I) that:
 - (a) comprises a claudin CAR (cell **adhesion** recognition) sequence; and
 - (b) contains 3-16 amino acid residues linked by peptide bonds;
- (2) a polynucleotide (II) encoding (I);
- (3) an expression vector (III) comprising (II);
- (4) a host cell (IV) transformed with (III);
- (5) a method (V) for detecting the presence of claudin expressing cells, comprising contracting a sample with an antibody that binds to a claudin comprising a CAR sequence and detecting the level of antibody-claudin complexes in the sample;
- (6) a kit for use in (V) comprising an antibody that binds to a claudin comprising a CAR sequence and a detection agent; and
- (7) a kit (VI) for enhancing drug delivery, comprising a skin patch and (I) (which inhibits claudin-mediated cell **adhesion**).

ACTIVITY - Cardiovascular; cytostatic; anti-angiogenic; neuroactive; dermatological; apoptotic.

MECHANISM OF ACTION - Antibody modulation (claimed) of claudin-mediated cell **adhesion**.

The mean electrical resistance across MDCK (Mandane Derby canine kidney) cell monolayers cultured for 24 hours in medium alone (control) or a medium containing Peptide 118 (Ac-WKIYSYAGDN-NH₂) at various concentrations was determined. It was found that Peptide 118 reduced the electrical resistance across the monolayer in a dose dependent manner (e.g. Control = 300 ohms/cm², 0.062 mg/ml of peptide = 250 ohms/cm² and 0.5 mg/ml of peptide = 10 ohms/cm²). This demonstrated the ability of Peptide 118 to inhibit the formation of tight junctions in epithelial cells.

USE - (I) may be used to modulate claudin-mediated cell **adhesion**, for decreasing undesirable claudin-mediated cell **adhesion**, for increasing vasopermeability in a mammal (by inhibiting claudin-mediated cell **adhesion**), for **treating** cancer by enhancing the delivery of a drug through the skin of a mammal, for enhancing the delivery of a drug to a tumor in a mammal, for inhibiting **angiogenesis**, for enhancing drug delivery to the nervous system, for enhancing wound healing, for enhancing **adhesion** of foreign tissue **implanted** within a mammal and for inducing apoptosis in cells that express claudin, for detecting cells that express claudin (claimed).

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Dwg.0/4

L20 ANSWER 19 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-270818 [23] WPIDS
DOC. NO. CPI: C2000-082527
TITLE: **Treating** bone defects with laminin 5,
useful particularly for periodontal disease, to
stimulate bone growth and regeneration, also to
stimulate bone marrow cells.
DERWENT CLASS: B04 D16
INVENTOR(S): TUCKER, B J
PATENT ASSIGNEE(S): (DESM-N) DESMOS INC
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000012690	A2	20000309	(200023)*	EN	14
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP US					
AU 9962409	A	20000321	(200031)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000012690	A2	WO 1999-US19773	19990827
AU 9962409	A	AU 1999-62409	19990827

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9962409	A Based on	WO 200012690

PRIORITY APPLN. INFO: US 1998-145387 19980901

AN 2000-270818 [23] WPIDS

AB WO 200012690 A UPAB: 20000516

NOVELTY - A method of **treating** a bone defect in a vertebrate, comprising administering to the affected bone, or to a tooth near periodontal bone, a composition containing laminin 5 (I), or its peptide, fragment or derivative, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method of stimulating periodontal bone growth, comprising applying to the bone, or an adjacent tooth, a composition containing (I) or its peptide, fragment or derivative;

(2) a composition containing (I) and a bone cement; and

(3) a method of stimulating growth and differentiation of bone marrow cells by contacting them with (I).

ACTIVITY - Antiarthritis; osteopathic; vulnerary; cytostatic; antiinfectious.

MECHANISM OF ACTION - (I) is an extracellular **matrix** component that promotes **adhesion** of epithelial cells.

USE - The method is used, particularly in humans, for **treating** bone or joint fractures, non-union, delayed union, percutaneous arthrodesis, pseudo-**arthritis** or -arthrosis, osteoporosis or osteogenesis imperfecta, but particularly

periodontal bone loss, e.g. associated with gingivitis and periodontal disease, also bone loss associated with trauma, tumors, infection, and degenerative diseases which are associated with skeletal mass, or integrity loss (claimed). (I) can also be used to induce regeneration of bone marrow in transplantation procedures. (I) can be used for improving **implantation**, stability or integration of prostheses and other **implants**, also to accelerate healing of ligament inserts or spine or other joint fusion procedures, and for ex vivo stimulation of bone growth for subsequent transplantation. Bone may be **treated** with an antibody, or other molecule that binds (I) specifically, to promote binding of endogenous (I).

ADVANTAGE - (I) increases the rate of bone formation and, when used in bone marrow transplantation, reduces the amount of donor marrow required.

Dwg.0/1

L20 ANSWER 20 OF 42 MEDLINE DUPLICATE 7
 ACCESSION NUMBER: 2000477389 MEDLINE
 DOCUMENT NUMBER: 20479730 PubMed ID: 11028759
 TITLE: An experimental study in the chick embryo chorioallantoic membrane of the anti-**angiogenic** activity of cyclosporine in rheumatoid **arthritis** versus osteoarthritis.
 AUTHOR: Ribatti D; Vacca A; Cantatore F P; Ria R; Benagiano V; Roncali L; Dammacco F
 CORPORATE SOURCE: Department of Human Anatomy and Histology, University of Bari, Medical School, Italy..
 ribatti@anatomia.uniba.it
 SOURCE: INFLAMMATION RESEARCH, (2000 Aug) 49 (8) 418-23.
 Journal code: B8U. ISSN: 1023-3830.
 PUB. COUNTRY: Switzerland
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200101
 ENTRY DATE: Entered STN: 20010322
 Last Updated on STN: 20010322
 Entered Medline: 20010125
 AB OBJECTIVE AND DESIGN: **Angiogenesis** plays an important role in the pathogenesis of rheumatoid **arthritis** (RA) and correlates with clinical score, synovial hyperplasia and infiltration of inflammatory cells. Many of the available **treatments** for RA have been shown to possess some degree of anti-**angiogenic** activity. Here, we studied the effect of cyclosporine, which exerts anti-**angiogenic** activity in vitro and in vivo [1] on **angiogenesis** induced in vivo in the chick embryo chorioallantoic membrane (CAM) by synovial RA and osteoarthritis (OA) tissues. MATERIAL AND METHODS: Wet synovial biopsies from 10 RA and 6 OA patients were **treated** with vehicle alone or with cyclosporine and **implanted** on the CAM at day 8 of incubation. On day 12, CAM tissues were assessed for the extent of **angiogenesis** and mononuclear cell infiltration. RESULTS: Cyclosporine inhibited **angiogenesis** and reduced the number of mononuclear cells in the CAM extracellular **matrix** only in RA **implants**. CONCLUSIONS: These data provide further evidence for a central role of new-formed blood vessels in

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RA. Moreover, cyclosporine on account of both its immunosuppressive and its anti-angiogenic activity can be proposed for the treatment of RA.

L20 ANSWER 21 OF 42 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2001367970 MEDLINE
DOCUMENT NUMBER: 21138867 PubMed ID: 11245278
TITLE: Local anti-angiogenic brain tumor
therapies.
AUTHOR: Sipos E P; Brem H
CORPORATE SOURCE: Division of Neurosurgery, Walter Reed Army Medical
Center Washington D.C., USA.
CONTRACT NUMBER: CA52857 (NCI)
SOURCE: JOURNAL OF NEURO-ONCOLOGY, (2000 Oct-Nov) 50 (1-2)
181-8. Ref: 93
Journal code: JCP; 8309335. ISSN: 0167-594X.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010702
Last Updated on STN: 20010702
Entered Medline: 20010628

AB The critical role of **angiogenesis** in the growth of solid tumors, including neoplasms of the central nervous system, has provided the impetus for research leading to the discovery of inhibitors of tumor neovascularization. The **therapeutic** potential of systemically administered **antiangiogenic** drugs for brain tumors, however, is limited by a variety of anatomic and physiologic barriers to drug delivery. **Implantable** controlled-release polymers for local drug administration directly into the tumor parenchyma have therefore been developed to achieve **therapeutic** concentrations of these drugs within the brain while minimizing systemic toxicity. With use of these polymers, successful **antiangiogenic therapy** for **treatment** of experimental intracranial malignancies has been achieved. This has been demonstrated with a variety of otherwise unrelated drugs -- including the angiostatic steroids, tetracycline derivatives, and amiloride -- which modulate collagenase activity, and thus, basement membrane and interstitial **matrix** metabolism. Controlled-release polymers provide a clinically practicable method of achieving sustained **antiangiogenic therapy** which can be readily used in combination with other **treatment** modalities such as cytoreductive surgery, radiation, and cytotoxic chemotherapy.

L20 ANSWER 22 OF 42 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 2000130051 MEDLINE
DOCUMENT NUMBER: 20130051 PubMed ID: 10664059
TITLE: Inhibition of corneal neovascularization by
alpha(v)-integrin antagonists in the rat.
AUTHOR: Klotz O; Park J K; Pleyer U; Hartmann C; Baatz H
CORPORATE SOURCE: Franz Volhard Clinic at Max Delbrück Center for
Molecular Medicine, Campus Buch, University Hospital
Charite, Berlin, Germany.

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SOURCE: GRAEFES ARCHIVE FOR CLINICAL AND EXPERIMENTAL
OPHTHALMOLOGY, (2000 Jan) 238 (1) 88-93.
Journal code: FPR; 8205248. ISSN: 0721-832X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000320
Last Updated on STN: 20000320
Entered Medline: 20000303

AB BACKGROUND: The **proliferation** of vascular endothelial cells and ultimately **angiogenesis** is inhibited by blocking integrin-mediated cell-matrix interaction. To assess the **therapeutic** potential of alpha(v)-integrin antagonists LM609 and cRGDfV in neovascularization of the anterior segment, their inhibitory effect on **angiogenesis** was studied in two rat models for corneal neovascularization. METHODS: Corneal neovascularization was induced in Wistar rats (n=51) either by silver nitrate burns or intrastromal **implantation** of polymer pellets containing 400 ng of fibroblast growth factor (bFGF). Animals were **treated** with subcutaneous injections of a cyclic alpha(v)-integrin antagonist (cRGDfV, 15 mg/kg body wt) or saline twice daily. Additional animals received intrastromal **implants** containing 400 ng bFGF together with either Lm609 (mAb, anti-alpha(v)beta(3)) or control antibody. Four days later, the animals were killed and the percentage of the surface area covered with vessels determined using digital image analysis. RESULTS: Systemic **treatment** with cRGDfV resulted in a significant reduction of corneal vessel growth in animals with bFGF-induced corneal vascularization. In corneas with silver nitrate burns, systemic cRGDfV **treatment** showed no significant reduction of vascularization compared with controls. Pellets containing bFGF and LM609 mAb induced significantly less neovascularization than pellets containing bFGF and control mAb. CONCLUSION: Our results suggest that in the rat cornea, alpha(v)beta(3) ligation does inhibit bFGF-induced neovascularization. A chemical burn of the cornea induces angiogenesis which is not inhibited by blocking alpha(v)-integrins. This suggests an **angiogenic** pathway independent of alpha(v)-integrins.

L20 ANSWER 23 OF 42 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 2001126565 MEDLINE
DOCUMENT NUMBER: 21074597 PubMed ID: 11206831
TITLE: Social isolation stress augments **angiogenesis**
induced by colon 26-L5 carcinoma cells in mice.
AUTHOR: Wu W; Murata J; Murakami K; Yamaura T; Hayashi K;
Saiki I
CORPORATE SOURCE: Department of Pathogenic Biochemistry, Institute of
Natural Medicine, Toyama Medical and Pharmaceutical
University, Japan.
SOURCE: CLINICAL AND EXPERIMENTAL METASTASIS, (2000) 18 (1)
1-10.
Journal code: DFC. ISSN: 0262-0898.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

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FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010222

AB We have previously shown that tumor necrosis factor-alpha (TNF-alpha), which is an important **angiogenesis**-related factor, was over-secreted in male BALB/c mice under social isolation stress as compared with the control, and closely associated with a remarkable elevation of tumor invasion and metastasis of colon 26-L5 carcinoma cells. In the present study, we explored the effect of isolation stress on the **angiogenesis** caused by colon 26-L5 carcinoma cells in vivo and in vitro. Social isolation lead to the enhancement of tumor growth after intrahepatic **implantation** with a fragment of colon 26-L5 tumor. **Angiogenic** response (number of vessels oriented towards tumor mass) and tumor growth (size) were significantly increased in the socially isolated mouse relative to that in the group-housed mice. Furthermore, higher protein level of hepatic TNF-alpha was found in the stressed mice than that in the control. Expression of mRNA for vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) were also elevated in the tumor regions and liver tissues of the stressed mice in comparison with that in group-housed mice. On the other hand, hepatic sinusoidal endothelial (HSE) cells **treated** with TNF-alpha exhibited a marked promotion of the migration, invasion, expression of mRNA for **matrix** metalloproteinase (MMP)-9, and tube-like formation, but no cytotoxicity against the cells in vitro. The above data suggest that the social isolation stress augmented the tumor-induced **angiogenesis** probably by up-regulating the **angiogenesis**-related factors, including TNF-alpha, VEGF and HGF, and consequently mediating the functions of endothelial cells such as migration, invasion, and tube-like formation.

L20 ANSWER 24 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-052684 [04] WPIDS
DOC. NO. CPI: C2000-013542
TITLE: Use of **angiogenic** factors to stimulate **angiogenesis** for **treatment** of cardiovascular diseases.
DERWENT CLASS: A96 B04 D16
INVENTOR(S): COLLEY, K J
PATENT ASSIGNEE(S): (ANGI-N) ANGIOGENIX INC
COUNTRY COUNT: 87
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9953943	A2	19991028	(200004)*	EN	37
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC					
MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES					
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK					
LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG					
SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
AU 9934955	A	19991108	(200014)		
BR 9909717	A	20001226	(200103)		
EP 1071445	A2	20010131	(200108)	EN	

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R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
NO 2000005190 A 20001130 (200108)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9953943	A2	WO 1999-US8420	19990416
AU 9934955	A	AU 1999-34955	19990416
BR 9909717	A	BR 1999-9717	19990416
		WO 1999-US8420	19990416
EP 1071445	A2	EP 1999-916697	19990416
		WO 1999-US8420	19990416
NO 2000005190	A	WO 1999-US8420	19990416
		NO 2000-5190	20001016

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9934955	A Based on	WO 9953943
BR 9909717	A Based on	WO 9953943
EP 1071445	A2 Based on	WO 9953943

PRIORITY APPLN. INFO: US 1998-82155P 19980417

AN 2000-052684 [04] WPIDS

AB WO 9953943 A UPAB: 20000124

NOVELTY - A method (A) of stimulating **angiogenesis** in humans/animals is new and comprises administering to the human/animal, a **therapeutically** effective amount of pleiotrophin (PTN) or midkine (MK) molecule in a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method (B) of stimulating **angiogenesis** in a human or animal in need comprises administering a **therapeutically** effective amount of an **angiogenic** factor in a pharmaceutically acceptable carrier comprising a silk elastin polyamino acid block copolymer; and

(2) a method of stimulating **angiogenesis** in a human or animal in need comprises administering a **therapeutically** effective amount of a gene transfer vector (which is preferably naked DNA or a viral vector) encoding pleiotrophin (PTN) or midkine (MK) protein, in a pharmaceutically acceptable carrier.

USE - The methods and compositions may be used in a variety of applications for wound healing and the **treatment** of burns. Wound healing applications include chronic cutaneous ulcers, bed or pressure sores (claimed), burns, and non-healing wounds. Wounds caused by trauma, e.g. by accident or surgery, may also be **treated**. Healing impaired or non-healing wounds may be **treated**, e.g. wounds associated with diabetes such as diabetic ulcers (claimed), as well as wounds occurring in immunosuppressed or immunocompromised patients, e.g. patients undergoing cancer **therapy**, AIDS patients, and medication-induced impaired wound healing. Other applications include vascularizing regions that have been cut off from blood supply secondary to prospective surgery or trauma, including general surgery, plastic surgery, and transplant surgery, or the

treatment of pre-gangrenous ischemic tissue or limb rescue. The methods may also be used to **treat** patients who are judged to be inoperable, due to surgical risk, poor health, or the diffuse nature of their disease, as well as in a variety of neurology and neurosurgery applications, e.g. for cerebrovascular diseases such as chronic vascular insufficiency in the brain, multi-infarct dementia, stroke and general brain ischemia (claimed). Other disease that may be **treated** include coronary artery disease; ischemic heart disease; diabetic peripheral vasculopathies; peripheral atherosclerotic disease (all claimed). Other applications include tissue repair and fortification, bone repair e.g. **treatment** of osteoporosis, cartilage repair, **treatment** of arthritis, and joint replacement or repair (all claimed), hair follicle targeting and **treatment** of hair loss, as well as skin repair.

ADVANTAGE - A need exists in the prior art for the development of methods for administering **angiogenic** growth factors such as pleiotrophin. The present invention provides these needs.

DESCRIPTION OF DRAWING(S) - The graph shows aggregate vessel cross sectional area over time after **treatment** of a mouse wound with an **implant** comprising pleiotrophin.
Dwg.2/2

L20 ANSWER 25 OF 42 MEDLINE DUPLICATE 11
 ACCESSION NUMBER: 2000005727 MEDLINE
 DOCUMENT NUMBER: 20005727 PubMed ID: 10537335
 TITLE: Interferon-alpha-mediated down-regulation of **angiogenesis**-related genes and **therapy** of bladder cancer are dependent on optimization of biological dose and schedule.
 AUTHOR: Slaton J W; Perrotte P; Inoue K; Dinney C P; Fidler I J
 CORPORATE SOURCE: Department of Cancer Biology, The University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.
 CONTRACT NUMBER: CA16672 (NCI)
 R29 CA67914 (NCI)
 R35-CA42107 (NCI)
 SOURCE: CLINICAL CANCER RESEARCH, (1999 Oct) 5 (10) 2726-34.
 Journal code: C2H; 9502500. ISSN: 1078-0432.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199911
 ENTRY DATE: Entered STN: 20000111
 Last Updated on STN: 20000111
 Entered Medline: 19991124
 AB The purpose of this study was to identify and optimize the **antiangiogenic** activity of IFN-alpha against human bladder cancer cells growing in the bladder of nude mice. 253J B-V IFN(R) cells (resistant to antiproliferative effects of IFN-alpha or IFN-beta) were **implanted** into the bladder wall of nude mice. Three days later, the mice were **treated** with s.c. injections of IFN-alpha (70,000 units/week) at different dosing schedules (1, 2, 3, or 7 times/week). Daily **therapy** with IFN-alpha produced the most significant inhibition of tumor growth; tumor vascularization, and down-regulation of basic fibroblast growth factor and **matrix** metalloprotease-9 mRNA and

protein expression. Changing dose and schedule of IFN-alpha administration had minimal effects on the expression of vascular endothelial growth factor or interleukin 8. The daily s.c. administrations of 5,000 or 10,000 units IFN-alpha-2a produced maximal inhibition of bFGF and MMP-9 expression (mRNA and protein), maximal reduction in tumor vessel density, and maximal reduction in serum levels of bFGF. Daily administration of higher doses of IFN-alpha failed to produce significant **antiangiogenic** effects. These data suggest that the **antiangiogenic** activity of IFN-alpha is dependent on frequent administration of optimal biological dose and not maximal tolerated dose.

L20 ANSWER 26 OF 42 MEDLINE DUPLICATE 12
 ACCESSION NUMBER: 2000036954 MEDLINE
 DOCUMENT NUMBER: 20036954 PubMed ID: 10567667
 TITLE: **Angiogenesis** in lipoma: An experimental study in the chick embryo chorioallantoic membrane.
 AUTHOR: Lucarelli E; Sangiorgi L; Benassi S; Donati D; Gobbi G A; Picci P; Vacca A; Ribatti D
 CORPORATE SOURCE: Laboratory of Oncology Research, Rizzoli Orthopedic Institute, 40136 Bologna, Italy.
 SOURCE: INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE, (1999 Dec) 4 (6) 593-6.
 Journal code: C8H; 9810955. ISSN: 1107-3756.
 PUB. COUNTRY: Greece
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200001
 ENTRY DATE: Entered STN: 20000124
 Last Updated on STN: 20000124
 Entered Medline: 20000110

AB Lipoma is one of the most common benign mesenchymal tumors. Its ability to trigger an **angiogenic** response is a critical step for its growth. Because adipose tissue serves as an important conduit for the vasculature, it is conceivable that the **angiogenic** properties of this tissue may modulate the growth of the vasculature in a paracrine manner. We investigated in vivo the **angiogenic** potential of bioptic fragments of human lipoma by using the chick embryo chorioallantoic membrane (CAM), a useful model for such an investigation. The **angiogenic** response in pathological and control **implants** was assessed on histologic sections by a morphometric method, 96 h after grafting. Results showed that pathological samples were surrounded by numerous allantoic vessels with a radially arranged pattern around the **implant**. The vascular counts in the CAMs **treated** with lipoma **implants** were comparable to that of FGF-2. The role played in vasoproliferative response by **angiogenic** cytokines (FGF-2, VEGF) released by adipocytes, by endogenous cytokines, such as FGF-2, stored in the CAM extracellular **matrix** and by **angiogenic** growth factors released by perivascular mononuclear cells around the newly-formed blood vessels, were supported by this study.

L20 ANSWER 27 OF 42 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 1999322174 EMBASE
 TITLE: Specific loss of chondromodulin-I gene expression in chondrosarcoma and the suppression of tumor

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angiogenesis and growth by its recombinant protein in vivo.
AUTHOR: Hayami T.; Shukunami C.; Mitsui K.; Endo N.; Tokunaga K.; Kondo J.; Takahashi H.E.; Hiraki Y.
CORPORATE SOURCE: Y. Hiraki, Dept. Molecular Interaction, Inst. Frontier Medical Sciences, Kyoto University, 53 Shongoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan
SOURCE: FEBS Letters, (1999) 458/3 (436-440).
Refs: 20
ISSN: 0014-5793 CODEN: FEBLAL
PUBLISHER IDENT.: S 0014-5793(99)01201-6
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Chondromodulin-I (ChM-I) was previously identified as an **angiogenesis** inhibitor in cartilage. Here, we demonstrated that the level of ChM-I transcripts was substantially reduced to 100 or even less in the lower-grade chondrosarcomas, in articular cartilage or other benign cartilage tumors. We **implanted** human chondrosarcoma OUMS-27 cells into nude mice that reproducibly produced tumors with cartilaginous **matrix**. Tumor-induced **angiogenesis** was evident when the tumors were excised 30 days after **implantation**. However, the local administration of recombinant human ChM-I almost completely blocked vascular invasion and tumor growth in vivo. Moreover, ChM-I also inhibited the growth of HT-29 colon adenocarcinoma in vivo, implying its **therapeutic** potential for solid tumors. Copyright (C) 1999 Federation of European Biochemical Societies.

L20 ANSWER 28 OF 42 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE
13

ACCESSION NUMBER: 1999263332 EMBASE
TITLE: Broad antitumor and **antiangiogenic** activities of AG3340, a potent and selective MMP inhibitor undergoing advanced oncology clinical trials.
AUTHOR: Shalinsky D.R.; Brekken J.; Zou H.; McDermott C.D.; Forsyth P.; Edwards D.; Margosiak S.; Bender S.; Truitt G.; Wood A.; Varki N.M.; Appelt K.
CORPORATE SOURCE: D.R. Shalinsky, Agouron Pharmaceuticals, Inc., 4245 Sorrento Valley Blvd., San Diego, CA 92121, United States. shalinsky@agouron.com
SOURCE: Annals of the New York Academy of Sciences, (1999) 878/- (236-270).
Refs: 72
ISSN: 0077-8923 CODEN: ANYAA
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We studied AG3340, a potent metalloproteinase (MMP) inhibitor with

pM affinities for inhibiting gelatinases (MMP-2 and -9), MT-MMP-1 (MMP-14), and collagenase-3 (MMP-13) in many tumor models. AG3340 produced dose-dependent pharmacokinetics and was well tolerated after intraperitoneal (i.p.) and oral dosing in mice. Across human tumor models, AG3340 produced profound tumor growth delays when dosing began early or late after tumor **implantation**, although all established tumor types did not respond to AG3340. A dose-response relationship was explored in three models: COLO-320DM colon, MV522 lung, and MDA-MB-435 breast. Dose-dependent inhibitions of tumor growth (over 12.5-200 mg/kg given twice daily, b.i.d.) were observed in the colon and lung models; and in a third (breast), maximal inhibitions were produced by the lowest dose of AG3340 (50 mg/kg, (b.i.d.) that was tested. In another model, AG3340 (100 mg/kg, once daily, i.p.) markedly inhibited U87 glioma growth and increased animal survival. AG3340 also inhibited tumor growth and increased the survival of nude mice bearing androgen-independent PC-3 prostatic tumors. In a sixth model, KKLS gastric, AG3340 did not inhibit tumor growth but potentiated the efficacy of Taxol. Importantly, AG3340 markedly decreased tumor **angiogenesis** (as assessed by CD-31 staining) and **cell proliferation** (as assessed by bromodeoxyuridine incorporation), and increased tumor necrosis and apoptosis (as assessed by hematoxylin and eosin and TUNEL staining). These effects were model dependent, but **angiogenesis** was commonly inhibited. AG3340 had a superior **therapeutic** index to the cytotoxic agents, carboplatin and Taxol, in the MV522 lung cancer model. In combination, AG3340 enhanced the efficacy of these cytotoxic agents without altering drug tolerance. Additionally, AG3340 decreased the number of murine melanoma (B16-F10) lesions arising in the lung in an intravenous metastasis model when given in combination with carboplatin or Taxol. These studies directly support the use of AG3340 in front-line combination chemotherapy in ongoing clinical trials in patients with advanced malignancies of the lung and prostate.

L20 ANSWER 29 OF 42 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1999007943 EMBASE

TITLE: Pharmacological reactivity of neoplastic and non-neoplastic associated neovasculature to vasoconstrictors.

AUTHOR: Andrade S.P.; Beraldo W.T.

CORPORATE SOURCE: Dr. S.P. Andrade, Campus Pampulha, Av. Antonio Carlos 6627, CEP 31270-901 Belo Horizonte-MG, Brazil.
andrades@mono.icb.ufmg.br

SOURCE: International Journal of Experimental Pathology, (1998) 79/6 (425-432).

Refs: 39

ISSN: 0959-9673 CODEN: IJEPEI

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy

LANGUAGE: English

SUMMARY LANGUAGE: English

AB **Angiogenesis** and the pharmacological responses of the tumour and non- tumour associated neovasculature have been investigated. Cannulated sponge discs in mice were used to host the **angiogenic** stimulators, while 133Xe washout was employed to assess local blood flow. Enhancement of blood flow was detected in

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implants bearing B16 cells, 3T3 cells and angiotensin II (AII)-**treated** at day 7. The responses of non-neoplastic associated neovasculature at day 14 post sponge **implantation** to the vasoconstrictors used endothelin-1 (Et-1), All, platelet activating factor (PAF) and 5- hydroxytryptamine (5-HT) were dose-dependent. By contrast, the newly formed blood vessels induced by tumour cells were markedly insensitive to the vasoconstrictors agonists Et-1 and All, while fully responsive to PAF and 5- HT. The vessels resulting from neoplastic stimulus exhibited altered pharmacological reactivity, suggesting that the characteristics of the neovasculature are dependent on the nature of the **angiogenic** stimuli.

L20 ANSWER 30 OF 42 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 1998:445028 SCISEARCH
THE GENUINE ARTICLE: ZN773
TITLE: Reduction in basic fibroblast growth factor mediated **angiogenesis** in vivo by linomide
AUTHOR: Nagler A (Reprint); Feferman R; Shoshan S
CORPORATE SOURCE: HADASSAH UNIV HOSP, DEPT BONE MARROW TRANSPLANTAT, JERUSALEM, ISRAEL (Reprint); HEBREW UNIV JERUSALEM, FAC MED DENT, DEPT ORAL BIOL, CONNECT TISSUE RES LAB, IL-91905 JERUSALEM, ISRAEL
COUNTRY OF AUTHOR: ISRAEL
SOURCE: CONNECTIVE TISSUE RESEARCH, (JUN 1998) Vol. 37, No. 1-2, pp. 61-68.
Publisher: GORDON BREACH SCI PUBL LTD, C/O STBS LTD, PO BOX 90, READING RG1 8JL, BERKS, ENGLAND.
ISSN: 0300-8207.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 39

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Linomide (N-phenylmethyl-1,2-dihydro-4-hydroxyl-1-methyl-2-oxoquinoline-3-carboxamide) is a novel immunomodulator with a potent anti-tumoral activity. This study was undertaken to test the effect of Linomide on basic fibroblast growth factor (bFGF) induced **angiogenesis** in vivo, which manifests itself in an increased number of blood vessels per unit of cell infiltrated area, Subcutaneously **implanted** polyvinyl alcohol sponges (PVS) in guinea pigs were used as a model system to quantitate **angiogenesis** in vivo. Oral **treatment** with Linomide was able to reduce significantly the bFGF induced blood vessel growth and proliferation within the **implanted** PVS, relative to untreated controls, In addition, Linomide significantly reduced the bFGF mediated augmentation of protein and collagen content in the **implanted** PVS, indicating an inhibition in the deposition of extracellular **matrix** (ECM). We conclude that the potent inhibition of bFGF induced **angiogenesis** by Linomide in vivo in addition to immunomodulatory effects may have potentially important clinical applications.

L20 ANSWER 31 OF 42 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 1998290827 MEDLINE
DOCUMENT NUMBER: 98290827 PubMed ID: 9625798
TITLE: **Angiogenesis** in hepatocellular carcinoma: an experimental study in the chick embryo

Searcher : Shears 308-4994

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chorioallantoic membrane.
AUTHOR: Marzullo A; Vacca A; Roncali L; Pollice L; Ribatti D
CORPORATE SOURCE: Institute of Pathology, University of Bari Medical
School, I-70124 Bari, Italy.
SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (1998 Jul) 13 (1)
17-21.
Journal code: CX5; 9306042. ISSN: 1019-6439.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980828
Last Updated on STN: 19980828
Entered Medline: 19980820

AB Ten samples of human hepatocellular carcinoma and three of a
laceration injure of the liver (controls) were grafted onto the
chick embryo chorioallantoic membrane (CAM) to investigate their
possible **angiogenic** activity. The **angiogenic**
response in pathological and control **implants** was assessed
on histologic sections by a morphometric method, 4 days after
grafting. The vascular count in the CAMs **treated** with the
pathological **implants** was significantly higher compared to
control ones and the **angiogenic** response induced by
pathological **implants** was comparable to that of a well
known **angiogenic** molecule, namely basic fibroblast growth
factor. The role played in vasoproliferative response by angio-genic
cytokines released by tumor cells, by CAM extracellular
matrix and by the perivascular mononuclear cells was
supported by this study.

L20 ANSWER 32 OF 42 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 97282975 MEDLINE
DOCUMENT NUMBER: 97282975 PubMed ID: 9137109
TITLE: Regulation of local host-mediated anti-tumor
mechanisms by cytokines: direct and indirect effects
on leukocyte recruitment and **angiogenesis**.
AUTHOR: Watanabe M; McCormick K L; Volker K; Ortaldo J R;
Wigginton J M; Brunda M J; Wilttrout R H; Fogler W E
CORPORATE SOURCE: Laboratory of Experimental Immunology, SAIC
Frederick, Maryland, USA.
SOURCE: AMERICAN JOURNAL OF PATHOLOGY, (1997 May) 150 (5)
1869-80.
Journal code: 3RS; 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970602
Last Updated on STN: 19970602
Entered Medline: 19970520

AB The regulation of tumor growth by cytokine-induced alterations in
host effector cell recruitment and activation is intimately
associated with leukocyte **adhesion** and **angiogenic**
modulation. In the present study, we have developed a novel tumor
model to investigate this complex series of events in response to
cytokine administration. Gelatin sponges containing recombinant

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human basic fibroblast growth factor (rhFGFb) and B16F10 melanoma cells were **implanted** onto the serosal surface of the left lateral hepatic lobe in syngeneic C57BL/6 mice. The tumor model was characterized by progressive tumor growth initially localized within the sponge and the subsequent development of peritoneal carcinomatosis. Microscopic examination of the sponge **matrix** revealed well developed tumor-associated vascular structures and areas of endothelial cell activation as evidenced by leukocyte margination. **Treatment** of mice 3 days after sponge **implantation** with a **therapeutic** regimen consisting of pulse recombinant human interleukin-2 (rhIL-2) combined with recombinant murine interleukin-12 (rmIL-12) resulted in a marked hepatic mononuclear infiltrate and inhibition of tumor growth. In contrast to the control group, sponges from mice **treated** with rhIL-2/rmIL-12 demonstrated an overall lack of cellularity and vascular structure. The regimen of rhIL-2 in combination with rmIL-12 was equally effective against gelatin sponge **implants** of rhFGFb/B16F10 melanoma in SCID mice **treated** with anti-asialo-GM1 in the absence of a mononuclear infiltration, suggesting that T, B, and/or NK cells were not the principal mediators of the anti-tumor response in this tumor model. The absence of vascularity within the sponge after **treatment** suggests that a potential mechanism of rhIL-2/rmIL-12 anti-tumor activity is the inhibition of neovascular growth associated with the establishment of tumor lesions. This potential mechanism could be dissociated from the known activities of these two cytokines to induce the recruitment and activation of host effector cells. Moreover, this model provides a unique opportunity to study the cellular and molecular mechanism(s) underlying both tumor **angiogenesis** and leukocyte recruitment to metastatic lesions.

L20 ANSWER 33 OF 42 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 97:48105 SCISEARCH
THE GENUINE ARTICLE: WA941
TITLE: Evaluation of omental **implantation** for perforated gastric ulcer **therapy**: Findings in a rat model
AUTHOR: Matoba Y (Reprint); Katayama H; Ohami H
CORPORATE SOURCE: SECOND HOSP, NIPPON MED SCH, CTR DIGEST DIS, NAKAHARA KU, 1-396 KOSUGI CHO, KAWASAKI, KANAGAWA 211, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: JOURNAL OF GASTROENTEROLOGY, (DEC 1996) Vol. 31, No. 6, pp. 777-784.
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010.
ISSN: 0944-1174.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: CLIN
LANGUAGE: English
REFERENCE COUNT: 17

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Omental **implantation**, a surgical procedure in which a perforated gastric or duodenal ulcer is repaired by drawing and **implanting** a portion of the omentum into the digestive tract, accelerates ulcer healing and inhibits ulcer recurrence. However, the mechanisms underlying these beneficial effects are

largely unknown. To clarify these mechanisms, we investigated ulcer healing in two groups of rats in which acetic acid-induced gastric ulcers were perforated. Omental **implantation** was used for repair in one group and simple suturing was employed in the other group. Greater anti inflammatory and **angiogenic** activity and accelerated collagen synthesis were seen in the omental **implantation** group. Basic fibroblast growth factor (bFGF)-mediated **angiogenesis** was noted in this group, as well as transforming growth factor-beta 1 (TGF-beta 1) activity within and around the omentum, resulting in abundant collagen production. It was confirmed that omental **implantation** accelerated ulcer healing and inhibited ulcer recurrence, and the presence of bFGF and TGF-beta 1 played a significant role in both these phenomena.

L20 ANSWER 34 OF 42 MEDLINE DUPLICATE 16
 ACCESSION NUMBER: 97202181 MEDLINE
 DOCUMENT NUMBER: 97202181 PubMed ID: 9049708
 TITLE: Angiotensin-II-induced **angiogenesis** in sponge **implants** in mice.
 AUTHOR: Andrade S P; Cardoso C C; Machado R D; Beraldo W T
 CORPORATE SOURCE: Department of Physiology and Biophysics, Federal University of Minas Gerais, Belo Horizonte, Brazil.
 SOURCE: INTERNATIONAL JOURNAL OF MICROCIRCULATION: CLINICAL AND EXPERIMENTAL, (1996 Nov-Dec) 16 (6) 302-7. Journal code: GSY; 8400122. ISSN: 0167-6865.
 PUB. COUNTRY: Switzerland
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199705
 ENTRY DATE: Entered STN: 19970609
 Last Updated on STN: 19980206
 Entered Medline: 19970527

AB Stimulators of **angiogenesis** hold potential in promoting the development of collateral circulation in ischaemic tissue and accelerating wound healing, but promote pathological vasoformation in **angiogenesis**-dependent diseases (solid tumours, atherosclerosis). The renin-angiotensin system is implicated in both beneficial **angiogenesis** and pathological vascular growth. We investigated the **angiogenic** activity of angiotensin II (AII) in a sponge **implant** model in mice; this peptide enhanced **angiogenesis**, as well as glycosaminoglycan (GAG, chondroitin sulfate proteoglycan) and protein synthesis in sponge **matrix** in mice in a dose-dependent fashion. Extensive **angiogenesis** was achieved with AII (1 microgram), which gave no significant increase in wet weight and protein and only a small effect on GAG. In the **implants treated** with AII (2 micrograms) no further increase in **angiogenesis** was observed, whereas a marked effect was shown in wet weight (326 +/- 15 vs. 424 +/- 27 mg), total protein (18 +/- 1 vs. 25 +/- 1 micrograms/ww) and GAG (98 +/- 10 vs. 160 +/- 13 ng/ww). The local blood flow has been determined by measuring the washout rate of ¹³³Xe injected into the **implants**, correlated with histological evidence of vessel growth. This model of **angiogenesis** has allowed sequential studies of fibrovascular tissue infiltration simultaneously with histological and biochemical parameters of **angiogenesis**.

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L20 ANSWER 35 OF 42 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1995:544867 BIOSIS

DOCUMENT NUMBER: PREV199698559167

TITLE: Effects of cryopreservation on the proliferation and anticoagulant activity of human saphenous vein endothelial cells.

AUTHOR(S): Bambang, L. S.; Mazzucotelli, J. P.; Moczar, M.; Beaujean, F.; Loisan, D. (1)

CORPORATE SOURCE: (1) Centre Recherches Chirurgicales Henri Mondor, Fac. Medecine, 8 rue General Sarrail, 94000 Creteil France

SOURCE: Journal of Thoracic and Cardiovascular Surgery, (1995) Vol. 110, No. 4 PART 1, pp. 998-1004. ISSN: 0022-5223.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Human saphenous veins were cryopreserved in 4% human albumin and 10% dimethyl sulfoxide. The effect of cryopreservation on endothelial cells was studied in terms of the anticoagulant activity of **thrombomodulin** and in terms of **cell proliferation**. After storage for 2 weeks at -150 degree C, 0.45 ± 0.07 times 10^{-5} endothelial cells/cm² were detected in cryopreserved veins and 1.03 ± 0.04 times 10^{-5} endothelial cells/cm² in fresh veins (p lt 0.01). The thrombin-catalyzed activation of protein C decreased after cryopreservation, indicating altered **thrombomodulin** activity in the endothelial cells. On a cell number basis, the release of soluble **thrombomodulin** was three times higher from the cryopreserved endothelium than from the fresh endothelium (p lt 0.05). The amount of spontaneous release of von Willebrand factor from the endothelial surface was not significantly different between fresh and cryopreserved veins. Endothelial cells were cultured from fresh veins and from their cryopreserved counterparts. On plating of endothelial cells in primary culture, the number of adhered cells was 0.9 ± 0.09 times 10^{-3} cells/cm² from fresh veins and 0.25 ± 0.03 times 10^{-3} cells/cm² from cryopreserved veins (p lt 0.01). The positive immunohistochemical stain for von Willebrand factor indicated that the endothelial cell character was maintained after cryopreservation. The endothelial desquamation with loss of anticoagulant function and the slow **proliferation** of surviving **cells** in vitro suggest an impaired endothelial healing in vivo. The loss of anticoagulant activity complicates the problems of the exposure of thrombogenic subendothelial **matrix** to blood in **implanted** cryopreserved veins.

L20 ANSWER 36 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 1993-320735 [40] WPIDS

DOC. NO. NON-CPI: N1993-247020

DOC. NO. CPI: C1993-142781

TITLE: Reconstructed cartilage tissue - cultured on a substrate, useful e.g. as model system to study cartilage structure, and to replace cartilage in joints.

DERWENT CLASS: B04 D16 P34

INVENTOR(S): KANDEL, R A

PATENT ASSIGNEE(S): (MOUN) MOUNT SINAI HOSPITAL CORP

COUNTRY COUNT: 22

Searcher : Shears 308-4994

09/822161

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9319168	A1	19930930	(199340)*	EN	35
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP RU US					
AU 9338816	A	19931021	(199407)		
US 5326357	A	19940705	(199426)		16
EP 631619	A1	19950104	(199506)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
JP 07505620	W	19950622	(199533)		10
AU 677953	B	19970515	(199728)		
EP 631619	B1	20000531	(200031)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
DE 69328776	E	20000706	(200039)		
ES 2146611	T3	20000816	(200044)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9319168	A1	WO 1993-CA111	19930318
AU 9338816	A	AU 1993-38816	19930318
US 5326357	A	US 1992-835831	19920318
EP 631619	A1	EP 1993-907686	19930318
		WO 1993-CA111	19930318
JP 07505620	W	JP 1993-516131	19930318
		WO 1993-CA111	19930318
AU 677953	B	AU 1993-38816	19930318
EP 631619	B1	EP 1993-907686	19930318
		WO 1993-CA111	19930318
DE 69328776	E	DE 1993-628776	19930318
		EP 1993-907686	19930318
		WO 1993-CA111	19930318
ES 2146611	T3	EP 1993-907686	19930318

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9338816	A Based on	WO 9319168
EP 631619	A1 Based on	WO 9319168
JP 07505620	W Based on	WO 9319168
AU 677953	B Previous Publ. Based on	AU 9338816
		WO 9319168
EP 631619	B1 Based on	WO 9319168
DE 69328776	E Based on	EP 631619
		WO 9319168
ES 2146611	T3 Based on	EP 631619

PRIORITY APPLN. INFO: US 1992-835831 19920318

AN 1993-320735 [40] WPIDS

AB WO 9319168 A UPAB: 19931129

Cartilage tissue (I) reconstituted in vitro having a biochemical compsn. and cellular and **matrix** organisation the same as animal articular cartilage tissue is new. (I) is characterised by a continuous layer of cartilage tissue and has an extracellular

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matrix comprising a superficial zone, in which chondrocytes are flattened and arranged parallel to the substrate, and mid and deep zones in which the chondrocytes are spherical, the **matrix** in the superficial, mid and deep zones contg. collagen fibres.

USE - (I) can be used as a model system for in vitro studies of cartilage structure, function and development. It is esp. useful for testing of pharmaceutical prepn. useful in the **treatment** of diseases of the joint, e.g. osteoarthritis, inflammatory arthropathies, septic **arthritis** and crystalline arthropathies. It may also be used to test **angiogenic** factors as it is normally resistant to vascular infiltration.

Dwg.0/8

ABEQ US 5326357 A UPAB: 19940817

Biological material comprising cartilage tissue reconstituted on a substrate in vitro from isolated chondrocytes characterised by a continuous layer of cartilage, having a substantial extracellular **matrix** comprises (a) a superficial zone in which the chondrocytes are flattened and arranged parallel to the substrate; (b) mid and deep zones where the chondrocytes are spherical, and the **matrix** is the superficial, mid and deep zones contains collage fibres.

USE - For prepn. of artificial cartilage tissue and reconstituted cartilage tissue for testing pharmaceutical prepn. for efficacy in **treatment** of diseases of the joints and as **implants** to replace or repair damaged or deficient cartilage.

Dwg.0/8

L20 ANSWER 37 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1993-078358 [10] WPIDS
DOC. NO. NON-CPI: N1993-060133
DOC. NO. CPI: C1993-034528
TITLE: Compsn. for **treating** bone defects -

contains **angiogenic** and osteogenic factors in **matrix**, esp. used with **matrix** stimulating cartilage growth.

DERWENT CLASS: B05 C03 D22 P34
INVENTOR(S): HUNZIKER, E B
PATENT ASSIGNEE(S): (SHAW-I) SHAW R F
COUNTRY COUNT: 41
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 530804	A1	19930310	(199310)*	EN	15
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
WO 9304710	A2	19930318	(199312)	EN	38
RW: OA					
W: AU BB BG BR CA CS FI HU JP KP KR LK MG MN MW NO PL RO RU SD					
ZA 9206729	A	19930526	(199328)		44
AU 9225411	A	19930405	(199330)		
US 5270300	A	19931214	(199350)		12
NO 9400764	A	19940429	(199426)		
WO 9304710	A3	19930415	(199512)		
JP 07500741	W	19950126	(199513)		
AU 657888	B	19950323	(199519)		
IL 102988	A	19980208	(199812)		

09/822161

NO 305784 B1 19990726 (199936)
BR 1100766 A3 19991019 (200013)#

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 530804	A1	EP 1992-115079	19920903
WO 9304710	A2	WO 1992-US6777	19920819
ZA 9206729	A	ZA 1992-6729	19920904
AU 9225411	A	AU 1992-25411	19920819
US 5270300	A	US 1991-756164	19910906
NO 9400764	A	WO 1992-US6777	19920819
		NO 1994-764	19940304
WO 9304710	A3	WO 1992-US6777	19920819
JP 07500741	W	WO 1992-US6777	19920819
		JP 1993-505209	19920819
AU 657888	B	AU 1992-25411	19920819
IL 102988	A	IL 1992-102988	19920828
NO 305784	B1	WO 1992-US6777	19920819
		NO 1994-764	19940304
BR 1100766	A3	BR 1997-1100766	19970512

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9225411	A Based on	WO 9304710
JP 07500741	W Based on	WO 9304710
AU 657888	B Previous Publ.	AU 9225411
	Based on	WO 9304710
NO 305784	B1 Previous Publ.	NO 9400764

PRIORITY APPLN. INFO: US 1991-756164 19910906; BR 1997-1100766
19970512

AN 1993-078358 [10] WPIDS

AB EP 530804 A UPAB: 19931122

Compsn. for **treating** bone defects comprises (1) a **matrix** (or **matrix**-forming material) to fill the defect; (2) an **angiogenic** factor (I) to stimulate formation and ingrowth of blood vessels and associated cells in the **matrix** and defect area, and (3) an osteogenic factor (II), with a delivery system, to cause cells in the **matrix** and defect to develop into bone cells.

Also new are kits for **treating** full thickness defects in joints consisting of this compsn. plus (a) a membrane (to prevent migration of cells from the bone defect side to the cartilage defect side) covering the **matrix**-filled region and sealed to the perimeter of the defect at the cartilage-bone junction and (b) a second **matrix** contg. a proliferation agent (III) to stimulate growth of repair cells; a chemotactic agent (IV) to attract such cells and (with a delivery system) transforming factor (V) to convert repair cells to chondrocytes. This second **matrix** is used to fill the cartilage portion fo the full thickness defect.

USE/ADVANTAGE - The compsns. and kits are used to **treat** and repair defects in cartilage and bone, esp. full-thickness defect seen in cases of severe osteoarthritis and other diseases and

injuries, but also superficial defects, and to improve stability/integration of **implanted** prostheses, etc. They are simple to apply to specific defect locations and efficiently induce growth of new tissue

Dwg. 0/0

ABEQ ZA 9206729 A UPAB: 19931116

Methods and compsn. are provided for the **treatment** and repair of defects in the cartilage or bone of humans and other animals as in full-thickness defects in joints. The defect in bone is filled with a **matrix** having pores large enough to allow cells to populate the **matrix** and to form blood vessels.

The **matrix** filling the bone defect contains an **angiogenic** factor and also contains an osteogenic factor in an appropriate delivery system. To induce cartilage formation, a defect in cartilage is filled with a **matrix** having pores sufficiently large to allow cartilage repair cells to populate the **matrix**. The **matrix** filling the defect in cartilage contains a proliferation agent and also contains a transforming factor in an appropriate delivery system. The **matrix** may also contain a chemotactic agent to attract cartilage repair cells.

In a full-thickness defect, the defect sites in bone and cartilage are separated from each other by a membrane, which is sealed to the cartilage-bone-junction and which prevents blood vessels and associated cells from penetrating from one side to the other.

ABEQ US 5270300 A UPAB: 19940203

Bone defects are **treated** using a mixt. of (A) a **matrix** (forming) material to fill a defect in bone; (B) an angiogenic factor present in (A) to stimulate the formation and ingrowth of blood vessels and associated cells in (A) and the area of defect, pref. bFGF opt. together with heparin in sulphate, TGF-B, PDGF-x, angiogenin and/or angiotropin and (C) an osteogenic factor associated with a delivery system, which is dissolved, suspended or emulsified in (A) and is present in sufficient concn. for subsequent delivery to bone repair cells to promote the cells to develop into bone cells which form bone.

The **matrix** pref. consists of fibrin, collagen, gelatin, agarose and/or Ca phosphate contg. cpds., (B) is pref. present to 5-10 ng/ml. (C) is pref. TGF-B associated with the delivery system and is present to 100 ng/ml.

USE/ADVANTAGE - A reliable **treatment** for cartilage in superficial cartilage defects, e.g. as found in the early stages of osteoarthritis, for **treatment** of cartilage or bone defects found in lesions of severe osteoarthritis and for **treatment** of other bone defects.

Dwg. 0/0

L20 ANSWER 38 OF 42 SCISEARCH COPYRIGHT 2001 ISI (R)

ACCESSION NUMBER: 93:335482 SCISEARCH

THE GENUINE ARTICLE: LD417

TITLE: A MODEL TO ASSESS INTERVENTIONS TO IMPROVE COLLATERAL BLOOD-FLOW - CONTINUOUS ADMINISTRATION OF AGENTS INTO THE LEFT CORONARY-ARTERY IN DOGS

AUTHOR: UNGER E F (Reprint); BANAI S; SHOU M; JAKLITSCH M; HODGE E; CORREA R; JAYE M; EPSTEIN S E

CORPORATE SOURCE: NHLBI, EXPTL PHYSIOL & PHARMACOL LAB, CARDIOL BRANCH, 9000 ROCKVILLE PIKE, BETHESDA, MD, 20892 (Reprint); RHONE POULENC RORER CENT RES, HORSHAM,

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PA, 00000
COUNTRY OF AUTHOR: USA
SOURCE: CARDIOVASCULAR RESEARCH, (MAY 1993) Vol. 27, No. 5,
pp. 785-791.
ISSN: 0008-6363.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 26

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective: The aim was to develop an experimental model in which **angiogenic** growth factor(s) could be targeted locally to enhance myocardial collateral formation. A preparation was developed in which agents could be infused selectively into the left main coronary artery on a chronic basis to assess the potential of acidic fibroblast growth factor (FGF) to improve collateral blood flow. Methods: Ameroid constrictors were placed on the left circumflex coronary artery of mixed hounds. Five weeks after ameroid placement, the artery was ligated and transected at the point of ameroid occlusion; a catheter was inserted and passed retrogradely into the left main coronary artery. The catheter was connected to an **implantable** infusion pump that provided continuous intracoronary drug infusion for 4 weeks. Dogs were randomised to receive acidic FGF with heparin (30 mug-h-1 and 30 IU.h-1, respectively, n=16) or heparin alone (30 IU.h-1, n=14). Regional myocardial blood flow was determined in the conscious state at the beginning and end of **treatment**. Results: There were no deaths or important surgical complications related to the establishment of the coronary artery infusions. During the **treatment** interval (5-9 weeks after ameroid placement) the ratio of maximum ischaemic zone/normal zone blood flow increased from 0.39(SD 0.10) to 0.50(0.11) ($p<0.01$) in dogs **treated** with acidic FGF plus heparin; however, similar improvement was noted in dogs **treated** with heparin alone. Ischaemic zone and normal zone vascular density was also equivalent in the two groups. Conclusions: This preparation makes possible the chronic intracoronary administration of agents which may promote myocardial **angiogenesis**, and allows assessment of collateral blood flow before and after **treatment**. As given in this investigation, acidic FGF had no demonstrable effect on collateral blood flow; however, this model may facilitate the identification of agents that do enhance myocardial collateral formation.

L20 ANSWER 39 OF 42 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 91:602364 SCISEARCH
THE GENUINE ARTICLE: GM349
TITLE: CHANGES IN BASIC FIBROBLAST GROWTH-FACTOR COINCIDENT WITH ESTRADIOL-INDUCED HYPERPLASIA OF THE ANTERIOR PITUITARIES OF FISCHER-344 AND SPRAGUE-DAWLEY RATS
AUTHOR: SCHECHTER J (Reprint); WEINER R
CORPORATE SOURCE: UNIV SO CALIF, SCH MED, DEPT ANAT & CELL BIOL, 1333 SAN PABLO ST, LOS ANGELES, CA, 90033 (Reprint); UNIV CALIF SAN FRANCISCO, CTR REPROD ENDOCRINOL, SAN FRANCISCO, CA, 94143
COUNTRY OF AUTHOR: USA
SOURCE: ENDOCRINOLOGY, (1991) Vol. 129, No. 5, pp. 2400-2408
DOCUMENT TYPE: Article; Journal

09/822161

FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 35

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Adult female Fischer 344 (F344) and Sprague-Dawley (SD) rats were treated with estradiol via Silastic implants for 10 and 20 days. This treatment period in F344 rats is sufficient to produce dramatic hyperplasia of anterior pituitary lactotropes, activation of folliculo-stellate cells (FS) as phagocytes, and reorganization of the blood supply, i.e. hemorrhagic lakes and arteriogenesis from vessels in the adjacent meninges. Estradiol-treated SD rats do not demonstrate a comparable response. We now report intense focal concentrations of cells immunopositive for basic fibroblast growth factor (FGF) in estradiol-treated F344 rats predominantly near the posterolateral edge of the anterior pituitary, a zone rich in gonadotropes and lactotropes. Immunostaining for FGF, by both light and electron microscopy, revealed that the immunopositive cells were gonadotropes, and that the immunoprecipitate was cytosolic and was most abundant in the cytosol facing the capillaries. Immunostaining for extracellular matrix-associated FGF also revealed foci of positivity at the postero-lateral edge. Estradiol-treated SD rats did not reveal comparable localization for FGF. Morphological analysis and immunolocalization of S-100 protein, a marker for FS cells, revealed that the periphery of the anterior pituitary of estradiol-treated F344 rats included numerous disrupted gonadotropes and, furthermore, was largely devoid of FS cells. This zone was more intact in control F344 rats, but lacked FS cells. The peripheral parenchyma of control and estradiol-treated SD rats was intact compared to that of F344 rats and consistently included FS cells. These results suggest that disruptions of gonadotropes at the pituitary periphery may release FGF, which could then stimulate angiogenesis from blood vessels within the adjacent meninges. The resultant systemic blood supply would stimulate lactotrope hypertrophy and hyperplasia. Since FS cells are known phagocytes within the anterior pituitary, their absence from the periphery of F344 rats may intensify or prolong the effect of the peripherally released FGF.

L20 ANSWER 40 OF 42 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 17
ACCESSION NUMBER: 1988:506826 BIOSIS
DOCUMENT NUMBER: BA86:127510
TITLE: FIBROBLAST GROWTH FACTOR EFFECTS ON PERIPHERAL NERVE REGENERATION IN A SILICONE CHAMBER MODEL.
AUTHOR(S): DANIELSEN N; PETTMANN B; VAHLSING H L; MANTHORPE M; VARON S
CORPORATE SOURCE: DEP. BIOL. M-001, UNIV. CALIF. SAN DIEGO, LA JOLLA, CALIF. 92093.
SOURCE: J NEUROSCI RES, (1988) 20 (3), 320-330.
CODEN: JNREDK. ISSN: 0360-4012.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB We have developed a silicone nerve regeneration chamber that is partitioned into two compartments by a strip of nitrocellulose paper. The modified two-compartment chamber allows the investigation of the effects on rat sciatic nerve regeneration of trophic or growth factors that are initially bound to the nitrocellulose partition. In this study we compared the effects of untreated

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nitrocellulose, a siliconized nitrocellulose strip, and a strip that had been soaked in a basic fibroblast growth factor (FGF) solution. FGF is a known **angiogenic** factor and a mitogen for endothelial cells, fibroblasts, and Schwann cells. All of these cell types are present in the peripheral nerve. In vitro analyses, using 3T3 cells as test cells, showed that some of the bound FGF remained active on the nitrocellulose paper for at least 8-10 days. In vivo experiments, examined at 16 days post-**implantation**, revealed that spatial migration of all cellular elements (perineurial-like cells, vasculature, and Schwann cells) across the chamber gap was slower with untreated nitrocellulose strips than with siliconized strips but was most advanced with FGF-**treated** ones. Most striking was the well-developed vascular arborization of the regenerate within the FGF chambers. Histologic sections from the proximal one-half of the chamber revealed that the regenerate in untreated strip chambers consisted of fibrin **matrix** and erythrocytes, whereas a well-developed structure with all the cellular elements of a regenerating nerve was seen in several of the FGF strip chambers. We conclude that FGF stimulates peripheral nerve regeneration in this model.

L20 ANSWER 41 OF 42 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
 ACCESSION NUMBER: 1986-291649 [44] WPIDS
 DOC. NO. NON-CPI: N1986-217776
 DOC. NO. CPI: C1986-126406
 TITLE: Purified protein with **angiogenic** activity
 - useful for promoting wound healing and in
 screening tests for malignancies.
 DERWENT CLASS: B04 D16 S03
 INVENTOR(S): FETT, J W; VALLEE, B L
 PATENT ASSIGNEE(S): (HARD) HARVARD COLLEGE
 COUNTRY COUNT: 5
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 8606079	A	19861023	(198644)*	EN	33
EP 220241	A	19870506	(198718)	EN	
JP 62502544	W	19871001	(198745)		
DK 8606056	A	19861216	(198803)		
US 4727137	A	19880223	(198811)		
US 4897464	A	19900130	(199012)		
EP 220241	B1	19931020	(199342)	EN	20
DE 3689191	G	19931125	(199348)		
JP 06062677	B2	19940817	(199431)		12
CA 1338453	C	19960709	(199638)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 8606079	A	WO 1986-US811	19860416
EP 220241	A	EP 1986-902741	19860416
JP 62502544	W	JP 1986-502329	19860416
US 4727137	A	US 1985-778387	19850920
US 4897464	A	US 1987-63252	19870625
EP 220241	B1	EP 1986-902741	19860416
		WO 1986-US811	19860416

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DE 3689191	G	DE 1986-3689191	19860416
		EP 1986-902741	19860416
JP 06062677	B2	WO 1986-US811	19860416
		JP 1986-502329	19860416
CA 1338453	C	WO 1986-US811	19860416
		CA 1986-506786	19860416

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 220241	B1 Based on	WO 8606079
DE 3689191	G Based on	EP 220241
	Based on	WO 8606079
JP 06062677	B2 Based on	JP 62502544
	Based on	WO 8606079

PRIORITY APPLN. INFO: US 1985-724088 19850417; US 1985-778387
19850920; US 1987-63252 19870625

AN 1986-291649 [44] WPIDS
AB WO 8606079 A UPAB: 19930922

A pore protein of human origin with **angiogenic** activity is claimed. It does not exhibit mitogenic activity toward 3T3 cells. Also claimed is a pure protein (I) of mol. wt. 12,500-17,500 dalton and isoelectric point greater than 9.5. A protein not having **angiogenic** activity of aminoacid sequence (II) is also new, is Glu-Asp-Asn-Ser-Arg-Tyr-Thr-His- Phe-Leu-Thr-Gln-His-Tyr-Asp-Ala Lys-Pro-Gln-Gly-Arg-Asp-Asp-Arg -Tyr-Cys-Glu-Ser-Ile-Met-Arg-Arg -Arg-Gly-Leu-Thr-Ser-Pro-Cys-Lys -Asp-Ile-Asn-Thr-Phe-Ile-His-Gly -Asn-Lys-Arg-Ser-Ile-Lys-Ala-Ile -Cys-Clu-Asn-Lys-Asn-Gly-Asn-Pro-His-Arg-Glu-Asn-Leu-Arg-Ile -Ser -Lys-Ser-Ser-Phe-Gln-Val-Thr-Thr -Cys-Lys-Leu-His-Gly-Gly-Ser-Pro -Trp-Pro-Phe-Cys-Gln-Tyr-Arg-Ala -Thr-Ala-Gly-Phe-Arg-Asn-Val-Val -Val-Ala-Cys-Glu-Asn-Gly-Leu-Pro -Val-His-Leu-Asp-Gln-Ser-Ile-Phe -Arg-Arg-Pro-OH.

In (II) at least one aminoacid has been chemically modified. The sequence represents angiogenin. (I) is characterised and claimed as follows: it is derived from human adenocarcinoma HT-29 cells having **angiogenic** activity, has a mol. wt. of 14,193 daltons as determined by aminoacid sequence analysis, has an isoelectric pt. greater than 9.5, lacks mitogenic activity toward 3T3 cells, and has ribonuclease activity. (I) thus has the characteristics of angiogenin itself.

USE - (I) may be administered to a mammal to promote development of a haemovascular network (claimed), e.g. to induce collateral circulation following a heart attack. Such **angiogenesis** factors play an important role in wound healing (e.g. at joints) and may also find applicability in the development of screening tests for malignancies. (I) may also be used to develop **angiogenesis** inhibitors which may be useful in the **treatment** of disorders associated with **angiogenesis**

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ABEQ US 4727137 A UPAB: 19930922

Pure protein having **angiogenic** activity is obtd. from a conditioned cell culture medium by (1) **treating** the medium to remove high mol. wt. proteins; (2) binding a portion of the **treated** medium to a cation exchange **matrix**; (3) eluting the bound portion from the **matrix**; (4)

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fractionating the eluate by high performance liq. chromatography; and (5) collecting the fraction contg. the protein.

The protein has purity such that 50 ng protein produces positive **angiogenic** response in the rabbit cornea implantation test.

Pref. the cells are human adenocarcinoma HT-29 cells and the protein has mol.wt. ca. 14193 daltons (by amino acid sequence analysis), isoelectric point above 9.5, no mitogenic activity toward 3T3 cells and ribonuclease activity.

USE - Obtd. proteins can be used in diagnosing malignancies, promoting wound healing, etc.

ABEQ US 4897464 A UPAB: 19930922

A substantially pure human protein has the amino acid sequence

1Glu-Asp-Asn-Ser-Arg-Tyr-Thr-His-Phe- Leu-Thr-Gln-His-Tyre.
15Asp-Ala-Lys-Pro-Gln-Gly-Arg-Asp -Asp-Arg-Tyr-Cys-Glu-Ser
Ile-30Meta-Arg-Arg-Arg-Gly-Leu-Thr-Ser- Pro-Cys-Lys-Asp-Ilem
Asn-Thr- 45-Phe-Ile- His-Gly-Asn-Lys-Arg-Ser- Ilee-Lys-Ala-Ile
Cys-Glu-Asn-60Lys-Asn-Gly-Asn-Pro-His- Arg-Glu-Asn-Leu-Arg-Ile-Ser
75Ser-Phe-Gln-Val-Thr-Thr-Cys-Lys-Leu His-Gly-GLy-Ser-Pro-Trp-
Pro-Pro-Cys- Gln-Tyr-Arg-Ala-Thr-Ala-Gly Phe-Arg- Asn-Val-Val-
105Val-Ala-Cys-Glu-Asn-Gly-Leu- Pro-Val-His-Leu-Asp-Gln-Ser-Ile-
120Phe-Arg-Arg-123Pro-OH

The protein is characterised in that about 50 ng of the protein produces a position **angiogenic** response in the rabbit cornea **implantation** test. USE - New protein has **angiogenic** activity.

ABEQ EP 220241 B UPAB: 19931202

A protein with antiogenic activity having the amino acid sequence:
(2).

Dwg.2/2

L20 ANSWER 42 OF 42 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1997:151980 BIOSIS

DOCUMENT NUMBER: PREV199799451183

TITLE: Angiotensin-II-induced **angiogenesis** in sponge **implants** in mice.

AUTHOR(S): Andrade, Silvia P. (1); Cardoso, Cibele C.; Machado, Rosangela D. P.; Beraldo, W. T.

CORPORATE SOURCE: (1) Dep. Physiol. Biophys., Inst. Biol. Sci., Federal Univ. Minas Gerais, Av. Antonio Carlos 6627, Cx Postal 486, Campus da Pampulha, 31270-901 Belo Horizonte, MG Brazil

SOURCE: International Journal of Microcirculation Clinical and Experimental, Vol. 16, No. 6, pp. 302-307.
ISSN: 0167-6865.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Stimulators of **angiogenesis** hold potential in promoting the development of collateral circulation in ischaemic tissue and accelerating wound healing, but promote pathological vasoformation in **angiogenesis**-dependent diseases (solid tumours, atherosclerosis). The renin-angiotensin system is implicated in both beneficial **angiogenesis** and pathological vascular growth. We investigated the **angiogenic** activity of angiotensin II (AII) in a sponge **implant** model in mice; this peptide enhanced **angiogenesis**, as well as glycosaminoglycan (GAG, chondroitin sulfate proteoglycan) and protein synthesis in sponge **matrix** in mice in a dose-dependent fashion. Extensive

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angiogenesis was achieved with AII (1 μ -g), which gave no significant increase in wet weight and protein and only a small effect on GAG. In the implants treated with AII (2 μ -g) no further increase in angiogenesis was observed, whereas a marked effect was shown in wet weight (326 \pm 15 vs. 424 \pm 27 mg), total protein (18 \pm 1 vs. 25 \pm 1 μ -g/ww) and GAG (98 \pm 10 vs. 160 \pm 13 ng/ww). The local blood flow has been determined by measuring the washout rate of ^{133}Xe injected into the implants, correlated with histological evidence of vessel growth. This model of angiogenesis has allowed sequential studies of fibrovascular tissue infiltration simultaneously with histological and biochemical parameters of angiogenesis.

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